Lechner K[1], Lechner B[2], Engel H[1], Halle M[1], Worm N[3], Scherr J[4]**

Vitamin D and Athletic Performance: Perspectives and Pitfalls

Vitamin D und Leistungssport: Perspektiven und Fallstricke

REVIEW

ACCEPTED: October 2019

PUBLISHED ONLINE: February 2020

DOI: 10.5960/dzsm.2019.404

Lechner K, Lechner B, Engel H, Halle M, Worm N*, Scherr J*. Vitamin D and athletic performance: perspectives and pitfalls. Dtsch Z Sportmed. 2020; 71: 35-42.

Summary

› **Vitamin D (VitD)** and its physiological function in regulating calcium/phosphorus absorption and bone remineralization were first described in the early 20th century. A better understanding of VitD signaling has advanced our understanding of the importance of adequate VitD status to human health and performance.

› **Tissues relevant to athletes** which depend on VitD for optimal function include innate and adaptive immune system, skeletal muscle, and bone. Cross-sectional studies have shown that more than half of athletes are deficient and/or insufficient in VitD. Correcting insufficiency, the suggested target of 25(OH)D blood levels above 30 ng/ml has the potential to optimize various aspects related to performance and regeneration in VitD insufficient athletes. This might help athletes to reach their full potential. Of note, there is no evidence pointing to actual or potential health risks of VitD levels within the recommended limits. VitD is therefore not on the list of prohibited substances of the world anti-doping agency.

› **To avoid toxicity,** VitD status should be monitored and supplementation strategies should be individualized and target-oriented. In terms of effectiveness and safety, low-dosed, continuous supplementation strategies of VitD are superior to intermittent application of supraphysiological boluses. The concept of synergy between nutrients lends qualified support to the assumption that VitD bioavailability and function depend on meal context and on the fat-soluble vitamins A and K2 as well as the minerals magnesium and zinc.

KEY WORDS:
Regeneration, Immune System, Muscular Function, Bone Health, Supplementation Strategies

Zusammenfassung

› **Vitamin D (VitD)** wurde als wichtiger Regulator der Kalzium/Phosphathomöostase und der Knochengesundheit zu Beginn des 20. Jahrhunderts erstbeschrieben. Seither hat sich unser Verständnis des VitD-Stoffwechsels, sowie der Bedeutung eines optimalen VitD-Status für Gesundheit und Leistungsfähigkeit deutlich erweitert.

› **Querschnittsstudien** haben gezeigt, dass die Mehrzahl der Leistungssportler niedrige VitD-Spiegel im Blut hat. Eine mangelhafte Versorgung mit VitD kann mit einer suboptimalen Funktion mehrerer Gewebe einhergehen, auf die der Sportler in besonderer Weise angewiesen ist, verbunden mit einer Einschränkung von Leistungsfähigkeit und Regeneration. Für den Athleten relevante Organe, welche für eine optimale Funktion in besonderem Maße VitD benötigen, beinhalten angeborenes und erworbenes Immunsystem, Skelettmuskel und Knochen. Die Korrektur eines mangelhaften VitD-Status (25(OH)D Zielwert im Blut größer 30 ng/ml) ist einer der Faktoren, welche Athleten dabei unterstützen können, ihr volles Potenzial auszuschöpfen. Erwähnenswert ist, dass kein Anhalt für potentielle Gesundheitsrisiken einer zielspiegeladaptierten Supplementationstherapie mit VitD besteht. VitD ist folgerichtig nicht auf der Liste verbotener Substanzen der Welt Anti-Doping Agentur aufgeführt.

› **Um Überdosierungen** und Toxizität zu vermeiden, sollte der VitD-Spiegel überwacht werden und Supplementationsstrategien personalisiert und zielspiegeladaptiert erfolgen. In Bezug auf Effektivität und Sicherheit sind niedrigdosierte, kontinuierliche Supplementationsstrategien der intermittierenden Einnahme von supraphysiologischen Bolusgaben überlegen. Überlegungen zur Bioverfügbarkeit und zum Konzept der Nährstoffsynergie lassen vermuten, dass die Einnahme von VitD idealerweise im Kontext einer fettreichen Mahlzeit sowie kombiniert mit den fettlöslichen Vitaminen A und K2 sowie den Mineralstoffen Magnesium und Zink erfolgen sollte.

SCHLÜSSELWÖRTER:
Regeneration, Immunsystem, Muskuläre Funktion, Knochengesundheit, Supplementationsstrategien

Introduction

"Like parachutes, which cannot prevent any injury while walking on the street (or when jumping from a motionless aircraft), vitamin D supplementation is not likely to be appropriate or useful in subjects without deficiency" (13).

Vitamin D (VitD) and its physiological function in regulating calcium/phosphorus absorption and bone remineralization was first described in the early 20th century (12). A more accurate delineation of VitD metabolism and signaling has significantly advanced our understanding of the importance of sufficient VitD levels to human health and ›

1. TECHNICAL UNIVERSITY MUNICH, *School of Medicine, Department of Prevention, Rehabilitation and Sports Medicine, Munich, Germany*
2. LUDWIG-MAXIMILIANS UNIVERSITY MUNICH, *Department of Internal Medicine IV, Munich, Germany*
3. GERMAN UNIVERSITY FOR PREVENTION AND HEALTH CARE MANAGEMENT, *Saarbrücken, Germany*
4. UNIVERSITY OF ZURICH, *University Center for Prevention and Sports Medicine, Balgrist University Hospital, Zurich, Switzerland*

**Contributed equally*

Article incorporates the Creative Commons Attribution – Non Commercial License.
https://creativecommons.org/licenses/by-nc-sa/4.0/

Scan QR Code and read article online.

CORRESPONDING ADDRESS:
Dr. med. Katharina Lechner
Technical University Munich
German Heart Centre
Department of Cardiology,
Lazarettstraße 36, 80636 Munich, Germany
: contact@katharinalechner.net

performance (20, 29, 34). There is solid evidence to suggest that some of VitD's newly identified skeletal and extra-skeletal functions are relevant to various facets of physical performance and regeneration (34). This collectively points to a potentially sports performance enhancing effect of maintaining VitD levels above the threshold of insufficiency. Of note, there is no evidence pointing to actual or potential health risks of VitD levels within this recommended threshold. VitD is therefore not on the WADA list of prohibited substances (29). Tissues particularly relevant to athletes, which depend on VitD for optimal function are bone (53) and extra-skeletal tissues such as innate (29) and/or adaptive immune system (9) and skeletal muscle (15).

The aim of this review is to provide perspective on (a) potential performance benefits of avoiding VitD insufficiency in athletes and (b) supplementation strategies. It is explicitly not meant to provide an exhaustive review of wider ranging benefits of optimal VitD levels.

Precautions when Interpreting the Results of Supplementation Studies

While epidemiology has linked 25(OH)D blood levels above the threshold of insufficiency (≥30 ng/ml) to reduced risk of musculoskeletal diseases, common cancers, autoimmune diseases, type 2 diabetes, cardiovascular disease, and infectious diseases (20), meta-analytic evidence on the effects of VitD supplementation has yielded mixed results (4, 27, 44). However, several aspects should provide caution against oversimplified inference when interpreting the conclusions derived from meta-analyses on supplementation studies (38). First, there is often significant heterogeneity with regard to dose and duration of supplementation, second, participants are often not recruited for deficiency and third, results are not analyzed for deficiency versus sufficiency which produces substantial overlaps in treatment versus placebo groups. Against this background, for the purpose of this narrative review, we primarily consider controlled clinical trials in athletes.

VitD Metabolism

VitD, unlike other vitamins, can be synthesized de novo by the body (20). Its synthesis involves 3 steps (graphically depicted in (22)): (a) conversion of 7-dehydrocholesterol to cholecalciferol in the skin following exposure to UVB radiation (b) hydroxylation of cholecalciferol to 25(OH)D=Calcidiol in the liver by the enzyme VitD-25-hydroxylase (25-OHase), and finally (c) activation to the metabolically active 1,25-(OH)2D=Calcitriol following a second hydroxylation by the enzyme 25(OH)D 1-α-hydroxylase (25(OH)D 1α-OHase) in the kidney (20). Of note, many tissues exhibit the cellular requirements for activation of 25(OH)D but only kidney cells (and granulomas in chronic granuloma-forming disorders) can export activated VitD into the circulation to meet systemic requirements (20).

25(OH)D is considered to be the storage form of VitD. Only activated VitD (1,25-(OH)2D), which is a secosteroid, interacts with target tissues by binding to the VitD nuclear receptor (VDR). The VDR is present in most tissues and the local production of VitD hormone constitutes an important regulator of gene transcription in body tissues such as – but not limited to – immune cells, skeletal muscle and bone (20, 29).

The major determinant of VitD status is exposure to sunlight, with 90% of VitD originating from a synthetic reaction in the skin following UVB radiation (29). VitD status – for which serum concentrations of 25(OH)D are a reasonable surrogate marker – depends on season, latitude, time of day, skin pigmentation, age, and sunscreen use (18, 20). As a rule of thumb, when an adult wearing a bathing suit is exposed to one minimal erythemal dose (MED, meaning the occurrence of a slight pinkness to the skin 24 h after exposure) of UVB radiation, the amount of VitD synthesized is equivalent to ingestion of 10.000-25.000 IU of VitD3 (20). Of note, ethnic groups with darker skin complexion need greater sunlight exposure to produce the same amount of VitD (20). Furthermore, age and sunscreen use both decrease the capacity of the skin to produce VitD (20); for example, sunscreen with a sun protection factor of 30 reduces VitD synthesis in the skin by more than 95% (20, 28). Relevant food sources of VitD in western dietary patterns are mostly negligible and limited to oily fish from the sea (and its organs such as cod liver oil) (20).

VitD Deficiency – Epidemiology

Above and below latitudes of about 33°, VitD synthesis in the skin is absent during the winter months (20). Because sunlight is the major source of VitD, the majority of non-supplemented elite athletes are exposed to low serum concentrations of 25(OH)D at this time of the year (10), in particular if sunlight exposure was low during the preceding summer months. Based on observations in the general population, it seems justified to speculate that many athletes might constantly exhibit insufficient VitD status (20). Low VitD status in athletes is associated with constraints in parameters relevant to performance and regeneration (as detailed further below). These can be improved by increasing VitD status above the threshold of insufficiency (10, 35).

VitD Status – Assessment

A surrogate marker to determine VitD status in clinical practice are serum concentrations of the inactive VitD metabolite 25(OH)D (20). According to the Endocrine Society clinical practice guideline, serum concentrations of 25(OH)D of 20 ng/ml or less are considered deficient, 21-29 ng/ml as insufficient, 30 ng/ml or greater as sufficient, 40-60 ng/ml (taking into account assay variability) as ideal, and up to 100 ng/ml as safe. Serum concentrations exceeding 150 ng/ml bear potential risk for toxicity (19, 21). Although there is no clear consensus over the optimal serum 25(OH)D concentration across general internal medicine and endocrine societies (40), we align with the recommendation of endocrine societies as we think that these tend to better reflect the totality of the evidence.

Pitfalls with Assessment of VitD Status

The Role of Ethnicity

Individuals of African-American descent often present with deficient 25(OH)D serum concentrations by current definition but without negative physiological consequences (7). These differences in 25(OH)D levels in ethnic groups with black vs white skin complexion are likely related to polymorphisms in VitD-binding protein (VDBP), resulting in lower concentrations of VDBP and total 25(OH)D but higher concentrations of free (bioavailable) VitD in Black Americans (42). Recent support for this concept originated from a study comparing polymorphic alleles of VDBP gene in 123 children and investigating relationships with serum 25(OH)D concentrations and daily VitD intake which demonstrated that VDBP genetic variability was associated with discriminatory differences in circulating concentrations of 25(OH)D at a given dose of VitD intake (32). Further to this

heterogeneity regarding VDBP genotype, there is evidence to suggest that Black Americans have higher parathyroid hormone, which enhances the activity of the enzyme 1-α-hydroxylase and inhibits 24 hydroxylase – the net effect being lower levels of total 25(OH)D, lower levels of the catabolite 24,25(OH)2D, but higher levels of the active metabolite 1,25 (OH)2D (7).

These considerations should be taken into account regarding supplementation strategies in athletes of African-American descent who do not seem to gain benefit from high levels of serum 25(OH)D (7) and highlight the need for more generalizable biomarkers of VitD status in different ethnic groups. Two strategies have been proposed in the literature to meet this need; first, free 25(OH)D as a marker that might be superior to total 25(OH)D in reflecting VitD status and potentially bone density across different ethnic groups (5) and second, VDBP genotyping as a potential way to inform public health recommendations concerning VitD supplementation strategies in racially/ethnically associated disparities (32). However, this is not a well-developed scientific area. Studies have yielded conflicting results and new assays require solid validation (including data on clinical endpoints) before they can be recommended for clinical practice (5).

The Role of Adiposity

In the general population, a graded relationship between VitD status and BMI, or more specifically adiposity, has been observed (41). Several hypotheses such as volumetric dilution and sequestration into adipose tissue have been proposed to underlie this observation of increased (relative) VitD deficiency with obesity (41). With regard to supplementation, in some but not all studies, adiposity has been negatively associated with the change in VitD status following VitD supplementation (41). Based on these considerations, adiposity should be taken into account when determining the dietary requirements for VitD in two distinct clinical situations in particular; first, "release" of VitD from fat mass in patients after bariatric surgery/with weight loss might result in rising 25(OH)D serum concentrations even without supplementation and second, sequestration into adipose tissue in overweight patients might attenuate the rise in serum 25(OH)D levels in this subgroup.

Other Factors

Certain medications such as glucocorticoids, anticonvulsant medications, and highly active antiretroviral therapy used to treat patients with acquired immunodeficiency syndrome (AIDS) interfere with VitD metabolism in that they increase catabolism of 25(OH)D and subsequent risk for VitD deficiency (20). This should be taken into consideration when treating athletes that take these medications.

VitD Supplementation Strategies

Substantial interindividual variation in VitD requirements justify personalized supplementation strategies that are tailored to the needs of each individual athlete. The following concepts might offer guidance in clinical practice:

1) target-oriented supplementation strategies with the aim of elevating VitD serum concentrations consistently above 30 ng/ml. To achieve this, the Endocrine Society Clinical Practice Guideline suggests at least 1500–2000 IU/d of VitD3 (20). Noteworthy, several factors beyond the dose administered impact on the change in 25(OH)D serum concentrations, including baseline serum concentration of 25(OH)D, body mass index (BMI), age, and serum albumin concentration (49). Based on these considerations, the following equation may assist in predicting the dose (in IU/day) of VitD needed to achieve a given change in 25(OH)D serum concentrations: Dose = [(8.52 - Desired change in serum 25(OH)D level in ng/ml) + (0.074 × Age) - (0.20 × BMI) + (1.74 × Albumin concentration) - (0.62 × Starting serum 25(OH) D concentration in ng/ml)]/(-0.002) (49).

2) low dosed, continuous supplementation strategies of VitD are superior to intermittent application of supraphysiological boluses in terms of effectiveness and safety. It is worth noting that bolus applications with supraphysiological boluses can lead to unintended consequences due to adverse effects on VitD signaling as discussed in detail further below (37).

3) close monitoring of 25(OH)D serum concentrations to avoid toxicity (29). This concept should be pursued in particular in medical conditions such as chronic granuloma-forming disorders (sarcoidosis or tubercolosis). In these conditions, caution is warranted because granulomas express high levels of 1α-hydroxylase which can result in overproduction of active VitD (24) and can lead to development of hypercalcemia in sarcoidosis patients (20). However, this should not deter physicians from supplementation if VitD deficiency is present (24) as those patients are also at high risk for deficiency (20).

4) it might be in the athlete's best interest to prevent VitD decline rather than waiting for deficiency and/or insufficiency. A reasonable strategy would be to test VitD levels at the end of summer when levels are highest and at the end of winter when levels are lowest.

5) Nutrients act in a coordinated manner in the body and optimal bioavailability (i.e., intestinal absorption) and subsequent metabolism of VitD depends on the availability of other nutrients. First, dietary fat (minimum 2g) is necessary to stimulate pancreatic lipase, which is needed for absorption of fat-soluble vitamins. Their bioavailability is thus significantly higher when consumed with dietary fat (8). Second, minerals like magnesium (51) and zinc (11) are necessary for VitD activation and VDR function respectively; magnesium is a cofactor in all enzymes that metabolize VitD and thus vital for activation of VitD (51) and zinc plays a role in VDR function and its intracellular concentrations impact on the activity of VitD dependent genes (11). This lends qualified support for the recommendation of ensuring adequate magnesium and zinc supply to obtain optimal bioavailability of VitD (26). Third, VitD works best in concert with other fat-soluble vitamins. Interaction of VitD with its receptor requires vitamin A (46, 47) and adequate supply with vitamin A could protect from VitD toxicity (30). This has been linked to vitamin A's ability to normalize the production of vitamin K-dependent proteins involved in tissue calcification such as matrix-Gla proteins (14). Vitamin K2 (VK2, also termed menaquinone (MK)), is a vital adjunct to VitD for preservation of bone structure (45) and is likely to protect soft tissues from calcification through its effects on matrix-Gla proteins which regulate tissue calcification (48). Studies investigating supplementation with MK-7 on progression of aortic valve calcification (25) and bicuspid aortic valve stenosis (39) are currently under way. Overall, it seems justified to argue in favor of choosing a VitD formulation that includes VK2 (e.g. 200 µg MK-7).

6) Although supplementation is a viable option to treat deficiency when de novo VitD production in the skin is very low or absent, it should be kept in mind that there are health benefits such as systemic endorphin production to sunlight exposure beyond VitD synthesis (6, 43).

7) Toxicity of VitD supplementation is highly unlikely if serum concentrations of 25(OH)D are monitored. ›

Avoid the Mindset "If Something is Good, More of It Is Better"

For reasons of time efficiency and compliance, concepts involving intermittent application of supraphysiological boluses of VitD are sometimes used in clinical practice. However, unintended consequences regarding VitD signaling have been observed with this strategy (37). In a study with 46 elite rugby players that were supplemented with 70.000 IU/week versus 35.000 IU/week for 12 weeks, adverse effects in the high-dose group were two-fold (37); first, following the bolus with 70.000 IU of VitD there was increased conversion to the inactive metabolite 24,25(OH)2D. This was associated with a decrease in the concentration and bioavailability of the active VitD metabolite 1,25(OH)2D. Second, elevated concentrations of the inactive metabolite 24,25(OH)2D persisted even after withdrawal and plummeting of serum concentrations of 25OHD and 1,25(OH)2D.

VitD – Mechanisms of Action Relevant to Athletic Performance

Cardiorespiratory fitness (CRF) is an important determinant of aerobic performance. In healthy adults (n=200, 54% women, mean age 40±14.4 years, mean VO2max 34±10.3 ml/kg/min), serum 25(OH)D concentration predicted CRF (positive correlation r=0.29, p=0.0001) after adjusting for age, gender and body mass index (2). Although the mechanism underlying this association is not fully clear, it seems plausible to speculate that one contributing factor might be improved immune- and muscular function/regeneration that ultimately translates to less training days lost to illness and injury as described below.

Immune Function

VitD is a potent regulator of the innate and adaptive immune system (9, 29) and plays a key role in controlling human T-cell antigen receptor signaling and activation (52). This implies a potential role of VitD in avoiding infections such as upper respiratory tract illness (URTI) which, from an athletic performance standpoint, means losing days of training and potentially days of competition.

One controlled clinical study examined the impact of VitD status on the incidence, severity and duration of URTI episodes in 225 endurance athletes during a 16-week winter training period (17). Plasma was analyzed for total 25(OH)D at baseline and at the end of the study. 38% of athletes at the start, and 55% at the end of study had levels of 12-20 ng/ml or <12 ng/ml plasma 25(OH)D concentrations respectively. In the group with <12 ng/ml plasma 25(OH)D concentrations, a significantly higher proportion of athletes presented with symptoms of URTI than in the group with optimal VitD concentrations (>48 ng/ml). Furthermore the number of days with URTI symptoms and the symptom-severity score in the VitD group <12 ng/ml was significantly higher. Interesting in this regard is that the optimal amount of circulating 25(OH)D in order to optimize immune function seemed to be higher than what is considered to be sufficient by the current guidelines (17).

In line with these results, another study which examined the effect of VitD supplementation on salivary immune function and symptoms of URTI in twenty-five male VitD-insufficient taekwondo athletes showed that a supplementation strategy with 5000 IU/day of VitD, compared to placebo during 4 weeks of winter training significantly increased serum 25(OH)D in the VitD group and change in serum 25(OH)D concentration was negatively associated with total URTI symptoms (23).

Collectively, these controlled clinical studies provide biological plausibility for the observation of an inverse association between circulating 25(OH)D and risk of URTI in athletes (29).

Muscle Preservation and Regeneration

Skeletal muscle is a direct target tissue of VitD (36). Myopathy, which includes muscle weakness and pain, is a prominent clinical feature of severe VitD deficiency syndrome (20), implying a potential role of VitD in muscular function.

A randomized controlled intervention trial in 20 healthy men with low 25(OH)D serum concentrations (<20 ng/ml) demonstrated that a supplementation strategy with 4000 IU/VitD3 daily for 6 weeks increased serum concentrations and compared to the placebo group, lead to improvements in invasively obtained markers of recovery, regeneration, and hypertrophy of skeletal muscle after high intensity eccentric muscle contractions (36). These data imply a role of VitD in reparative processes in skeletal muscle, which can beneficially impact on skeletal muscle hypertrophy when serum concentrations of VitD are above the threshold of insufficiency (36).

These results align with observational data implying an association between 25(OH)D serum concentrations and functional recovery of skeletal muscle after eccentric muscle contractions in humans (3).

Future Directions – Potential Role of VitD in Muscle Fuel Availability

Experimental evidence from cell cultures (1) and observations from short-term supplementation studies with VitD in humans (31, 33) suggest that VitD plays an important role in regulating skeletal muscle insulin sensitivity. This has been linked to insulin-like effects of VitD (1) and to VitD's role in calcium homeostasis, which contributes to regulation of GLUT-4 expression (16). It thus provides a mechanistic base for the observation of improved glycemic control/insulin sensitivity in individuals with diabetes following VitD supplementation (31, 33). Collectively, VitD's effect on muscular insulin-dependent glucose uptake (16), combined with VitD's effect on mitochondrial bioenergetics/oxidative function (50) leads one to speculate that increasing VitD status above the threshold of deficiency might potentially enhance exercise performance in athletes, particularly in endurance sports where VitD's effect on glucose uptake into muscle cells may result in increased fuel availability and/or avoid decrements in fuel metabolism during exercise.

Bone Health

Bone health, because of VitD's role in regulating calcium/phosphorus absorption and bone remineralization, is the classical tissue associated with VitD (20). As a metabolically active tissue, bone remodels in response to different stimuli and research has implicated that VitD might be involved in many aspects of this remodeling process. This might offer some biological plausibility for the observation of decreased risk of stress fractures with optimal VitD serum concentrations in athletes (29).

Take-Home Messages

Overall, the evidence shows that 25(OH)D blood levels should be maintained above 20 ng/ml (deficiency) for prevention of osteomalacia (20). However, ideal effects on

bone-, muscle-, and immune function are achieved when 25(OH)D blood levels are above the threshold of insufficiency (≥30 ng/ml) (17, 20).

Cross-sectional studies have shown that more than half of elite athletes are deficient and/or insufficient in VitD during winter months (10) and observations in the general population lead one to speculate that many athletes might be exposed to insufficient 25(OH)D levels year round (20). Insufficient VitD status is associated with unfavorable consequences on function of tissues relevant to performance and regeneration. The best evidence exists for immune-, skeletal muscle- and bone health, the latter particularly in non-weight bearing athletes, where the osteogenic stimulus of resistance training is absent (29, 35).

Only screening for insufficiency can detect the substantial subgroup who is deficient or insufficient in VitD and who could benefit from supplementation. Therefore it might be worth considering adding biomarkers indicative of VitD status to screening evaluation in athletes. Whether free 25(OH)D is superior to total 25(OH)D in reflecting VitD status is currently being investigated, as is the potential role of VDBP genotyping in guiding VitD dosage recommendations in racial/ethnic disparities.

Greatest benefit is derived from avoiding VitD insufficiency. Although there are indications where being above the threshold of insufficiency might potentially confer benefit (17, 20), elevating 25(OH)D above the suggested target range of 40-60 ng/ml is not likely to yield significant extra benefit (22). In this regard, the quest for optimization should not tempt one to forget the first do no harm principle. If something is good, more of it is not necessarily better and the potential for side effects should provide precaution against supplementing with supraphysiological doses of isolated VitD that are larger than those that provide clear benefits.

Supplementation strategies should be personalized and target-oriented, and VitD status should be monitored. 25(OH)D serum concentrations of 30-60 ng/ml are considered save and are associated with better immune-, muscle- und bone function in athletes. Suboptimal VitD status might result in missed opportunities for athletes to reach their full potential. This should facilitate cost benefit considerations with respect to monitoring VitD status and, as appropriate, pursuing supplementation strategies.

The concept of synergy between nutrients lends qualified support for the assumption that it might be in the athlete's best interest to ensure adequate supply with vitamins A and K2 and minerals magnesium and zinc along with VitD supplementation. Furthermore, VitD should be consumed in the context of a fat-based meal for intestinal bioavailability.

Conflict of Interest

The authors have no conflict of interest.

References

(1) **ANTINOZZI C, CORINALDESI C, GIORDANO C, PISANO A, CERBELLI B, MIGLIACCIO S, DI LUIGI L, STEFANANTONI K, VANNELLI GB, MINISOLA S, VALESINI G, RICCIERI V, LENZI A, CRESCIOLI C.** Potential role for the VDR agonist elocalcitol in metabolic control: Evidences in human skeletal muscle cells. J Steroid Biochem Mol Biol. 2017; 167: 169-181. doi:10.1016/j.jsbmb.2016.12.010

(2) **ARDESTANI A, PARKER B, MATHUR S, CLARKSON P, PESCATELLO LS, HOFFMAN HJ, POLK DM, THOMPSON PD.** Relation of vitamin D level to maximal oxygen uptake in adults. Am J Cardiol. 2011; 107: 1246-1249. doi:10.1016/j.amjcard.2010.12.022

(3) **BARKER T, HENRIKSEN VT, MARTINS TB, HILL HR, KJELDSBERG CR, SCHNEIDER ED, DIXON BM, WEAVER LK.** Higher serum 25-hydroxyvitamin D concentrations associate with a faster recovery of skeletal muscle strength after muscular injury. Nutrients. 2013; 5: 1253-1275. doi:10.3390/nu5041253

(4) **BOLLAND MJ, GREY A, AVENELL A.** Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. Lancet Diabetes Endocrinol. 2018; 6: 847-858. doi:10.1016/S2213-8587(18)30265-1

(5) **BOUILLON R.** Free or Total 25OHD as Marker for Vitamin D Status? J Bone Miner Res. 2016; 31: 1124-1127. doi:10.1002/jbmr.2871

(6) **BOUILLON R, MARCOCCI C, CARMELIET G, BIKLE D, WHITE JH, DAWSON-HUGHES B, LIPS P, MUNNS CF, LAZARETTI-CASTRO M, GIUSTINA A, BILEZIKIAN J.** Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions. Endocr Rev. 2019; 40: 1109-1151. doi:10.1210/er.2018-00126

(7) **BROWN LL, COHEN B, TABOR D, ZAPPALÀ G, MARUVADA P, COATES PM.** The vitamin D paradox in Black Americans: a systems-based approach to investigating clinical practice, research, and public health - expert panel meeting report. BMC Proc. 2018; 12: 6. doi:10.1186/s12919-018-0102-4

(8) **BROWN MJ, FERRUZZI MG, NGUYEN ML, COOPER DA, ELDRIDGE AL, SCHWARTZ SJ, WHITE WS.** Carotenoid bioavailability is higher from salads ingested with full-fat than with fat-reduced salad dressings as measured with electrochemical detection. Am J Clin Nutr. 2004; 80: 396-403. doi:10.1093/ajcn/80.2.396

(9) **CHUN RF, LIU PT, MODLIN RL, ADAMS JS, HEWISON M.** Impact of vitamin D on immune function: lessons learned from genome-wide analysis. Front Physiol. 2014; 5: 151. doi:10.3389/fphys.2014.00151

(10) **CLOSE GL, RUSSELL J, COBLEY JN, OWENS DJ, WILSON G, GREGSON W, FRASER WD, MORTON JP.** Assessment of vitamin D concentration in non-supplemented professional athletes and healthy adults during the winter months in the UK: implications for skeletal muscle function. J Sports Sci. 2013; 31: 344-353. doi:10.1080/02640414.2012.733822

(11) **CRAIG TA, BENSON LM, NAYLOR S, KUMAR R.** Modulation effects of zinc on the formation of vitamin D receptor and retinoid X receptor α-DNA transcription complexes: analysis by microelectrospray mass spectrometry. Rapid Commun Mass Spectrom. 2001; 15: 1011-1016. doi:10.1002/rcm.332

(12) **DE LUCA HF.** History of the discovery of vitamin D and its active metabolites. Bonekey Rep. 2014; 3: 479. doi:10.1038/bonekey.2013.213

(13) **FASSIO A, ROSSINI M, GATTI D.** Vitamin D: no efficacy without deficiency. What's new? Reumatismo. 2019; 71: 57-61. doi:10.4081/reumatismo.2019.1201

(14) **FU X, WANG XD, MERNITZ H, WALLIN R, SHEA MK, BOOTH SL.** 9-Cis retinoic acid reduces 1alpha,25-dihydroxycholecalciferol-induced renal calcification by altering vitamin K-dependent gamma-carboxylation of matrix gamma-carboxyglutamic acid protein in A/J male mice. J Nutr. 2008; 138: 2337-2341. doi:10.3945/jn.108.093724

(15) **GIRGIS CM, CLIFTON-BLIGH RJ, HAMRICK MW, HOLICK MF, GUNTON JE.** The roles of vitamin D in skeletal muscle: form, function, and metabolism. Endocr Rev. 2013; 34: 33-83. doi:10.1210/er.2012-1012

(16) **GIRGIS CM, CLIFTON-BLIGH RJ, TURNER N, LAU SL, GUNTON JE.** Effects of vitamin D in skeletal muscle: falls, strength, athletic performance and insulin sensitivity. Horumon To Rinsho. 2014; 80: 169-181. doi:10.1111/cen.12368

(17) **HE CS, HANDZLIK M, FRASER WD, MUHAMAD A, PRESTON H, RICHARDSON A, GLEESON M.** Influence of vitamin D status on respiratory infection incidence and immune function during 4 months of winter training in endurance sport athletes. Exerc Immunol Rev. 2013; 19: 86-101.

(18) **HOLICK MF.** Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr. 2004; 80: 1678S-1688S. doi:10.1093/ajcn/80.6.1678S

(19) **HOLICK MF.** Vitamin D Deficiency. N Engl J Med. 2007; 357: 266-281. doi:10.1056/NEJMra070553

(20) **HOLICK MF, BINKLEY NC, BISCHOFF-FERRARI HA, GORDON CM, HANLEY DA, HEANEY RP, MURAD MH, WEAVER CM; ENDOCRINE SOCIETY.** Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011; 96: 1911-1930. doi:10.1210/jc.2011-0385

(21) **HOLICK MF, BINKLEY NC, BISCHOFF-FERRARI HA, GORDON CM, HANLEY DA, HEANEY RP, MURAD MH, WEAVER CM.** Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. J Clin Endocrinol Metab. 2012; 97: 1153-1158. doi:10.1210/jc.2011-2601

(22) **HOSSEIN-NEZHAD A, HOLICK MF.** Vitamin D for health: a global perspective. Mayo Clin Proc. 2013; 88: 720-755. doi:10.1016/j.mayocp.2013.05.011

(23) **JUNG HC, SEO M-W, LEE S, KIM SW, SONG JK.** Vitamin D3 Supplementation Reduces the Symptoms of Upper Respiratory Tract Infection during Winter Training in Vitamin D-Insufficient Taekwondo Athletes: A Randomized Controlled Trial. Int J Environ Res Public Health. 2018; 15: 2003. doi:10.3390/ijerph15092003

(24) **KAMPHUIS LS, BONTE-MINEUR F, VAN LAAR JA, VAN HAGEN PM, VAN DAELE PL.** Calcium and vitamin D in sarcoidosis: is supplementation safe? Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2014; 29: 2498-2503, 2014.

(25) **LINDHOLT JS, FRANDSEN NE, FREDGART MH, ØVREHUS KA, DAHL JS, MØLLER JE, FOLKESTAD L, URBONAVICIENE G, BECKER SW, LAMBRECHTSEN J, AUSCHER S, HOSBOND S, ALAN DH, RASMUSSEN LM, GERKE O, MICKLEY H, DIEDERICHSEN A.** Effects of menaquinone-7 supplementation in patients with aortic valve calcification: study protocol for a randomised controlled trial. BMJ Open. 2018; 8: e022019. doi:10.1136/bmjopen-2018-022019

(26) **MAKTABI M, JAMILIAN M, ASEMI Z.** Magnesium-Zinc-Calcium-Vitamin D Co-supplementation Improves Hormonal Profiles, Biomarkers of Inflammation and Oxidative Stress in Women with Polycystic Ovary Syndrome: a Randomized, Double-Blind, Placebo-Controlled Trial. Biol Trace Elem Res. 2018; 182: 21-28. doi:10.1007/s12011-017-1085-0

(27) **MARTINEAU AR, JOLLIFFE DA, HOOPER RL, GREENBERG L, ALOIA JF, BERGMAN P, DUBNOV-RAZ G, ESPOSITO S, GANMAA D, GINDE AA, GOODALL EC, GRANT CC, GRIFFITHS CJ, JANSSENS W, LAAKSI I, MANASEKI-HOLLAND S, MAUGER D, MURDOCH DR, NEALE R, REES JR, SIMPSON S JR, STELMACH I, KUMAR GT, URASHIMA M, CAMARGO CA JR.** Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. 2017; 356: i6583. doi:10.1136/bmj.i6583

(28) **MATSUOKA LY, IDE L, WORTSMAN J, MACLAUGHLIN JA, HOLICK MF.** Sunscreens suppress cutaneous vitamin D3 synthesis. J Clin Endocrinol Metab. 1987; 64: 1165-1168. doi:10.1210/jcem-64-6-1165

(29) **MAUGHAN RJ, BURKE LM, DVORAK J, LARSON-MEYER DE, PEELING P, PHILLIPS SM, RAWSON ES, WALSH NP, GARTHE I, GEYER H, MEEUSEN R, VAN LOON LJC, SHIRREFFS SM, SPRIET LL, STUART M, VERNEC A, CURRELL K, ALI VM, BUDGETT RG, LJUNGQVIST A, MOUNTJOY M, PITSILADIS YP, SOLIGARD T, ERDENER U, ENGEBRETSEN L.** IOC consensus statement: dietary supplements and the high-performance athlete. Br J Sports Med. 2018; 52: 439-455. doi:10.1136/bjsports-2018-099027

(30) **MERNITZ H, SMITH DE, WOOD RJ, RUSSELL RM, WANG XD.** Inhibition of lung carcinogenesis by 1alpha,25-dihydroxyvitamin D3 and 9-cis retinoic acid in the A/J mouse model: evidence of retinoid mitigation of vitamin D toxicity. Int J Cancer. 2007; 120: 1402-1409. doi:10.1002/ijc.22462

(31) **NASRI H, BEHRADMANESH S, MAGHSOUDI AR, AHMADI A, NASRI P, RAFIEIAN-KOPAEI M.** Efficacy of supplementary vitamin D on improvement of glycemic parameters in patients with type 2 diabetes mellitus; a randomized double blind clinical trial. J Renal Inj Prev. 2013; 3: 31-34.

(32) **NEWTON DA, BAATZ JE, KINDY MS, GATTONI-CELLI S, SHARY JR, HOLLIS BW, WAGNER CL.** Vitamin D binding protein polymorphisms significantly impact vitamin D status in children. Pediatr Res. 2019 [Epub ahead of print]. doi:10.1038/s41390-019-0322-y

(33) **NIKOOYEH B, NEYESTANI TR, FARVID M, ALAVI-MAJD H, HOUSHIARRAD A, KALAYI A, SHARIATZADEH N, GHARAVI A, HERAVIFARD S, TAYEBINEJAD N, SALEKZAMANI S, ZAHEDIRAD M.** Daily consumption of vitamin D- or vitamin D + calcium-fortified yogurt drink improved glycemic control in patients with type 2 diabetes: a randomized clinical trial. Am J Clin Nutr. 2011; 93: 764-771. doi:10.3945/ajcn.110.007336

(34) **OWENS DJ, ALLISON R, CLOSE GL.** Vitamin D and the Athlete: Current Perspectives and New Challenges. Sports Med. 2018; 48: 3-16. doi:10.1007/s40279-017-0841-9

(35) **OWENS DJ, FRASER WD, CLOSE GL.** Vitamin D and the athlete: emerging insights. Eur J Sport Sci. 2015; 15: 73-84. doi:10.1080/17461391.2014.944223

(36) **OWENS DJ, SHARPLES AP, POLYDOROU I, ALWAN N, DONOVAN T, TANG J, FRASER WD, COOPER RG, MORTON JP, STEWART C, CLOSE GL.** A systems-based investigation into vitamin D and skeletal muscle repair, regeneration, and hypertrophy. Am J Physiol Endocrinol Metab. 2015; 309: E1019-E1031. doi:10.1152/ajpendo.00375.2015

(37) **OWENS DJ, TANG JC, BRADLEY WJ, SPARKS AS, FRASER WD, MORTON JP, CLOSE GL.** Efficacy of High-Dose Vitamin D Supplements for Elite Athletes. Med Sci Sports Exerc. 2017; 49: 349-356. doi:10.1249/MSS.0000000000001105

(38) **PACKER M.** Are Meta-Analyses a Form of Medical Fake News? Thoughts About How They Should Contribute to Medical Science and Practice. Circulation. 2017; 136: 2097-2099. doi:10.1161/CIRCULATIONAHA.117.030209

(39) **PEETERS FECM, VAN MOURIK MJW, MEEX SJR, BUCERIUS J, SCHALLA SM, GERRETSEN SC, MIHL C, DWECK MR, SCHURGERS LJ, WILDBERGER JE, CRIJNS HJGM, KIETSELAER BLJH.** Bicuspid Aortic Valve Stenosis and the Effect of Vitamin K2 on Calcification Using (18)F-Sodium Fluoride Positron Emission Tomography/Magnetic Resonance: The BASIK2 Rationale and Trial Design. Nutrients. 2018; 10: 386. doi:10.3390/nu10040386

(40) **PILZ S, ZITTERMANN A, TRUMMER C, THEILER-SCHWETZ V, LERCHBAUM E, KEPPEL MH, GRÜBLER MR, MÄRZ W, PANDIS M.** Vitamin D testing and treatment: a narrative review of current evidence. Endocr Connect. 2019; 8: R27-R43. doi:10.1530/EC-18-0432

(41) **POURSHAHIDI LK.** Vitamin D and obesity: current perspectives and future directions. Proc Nutr Soc. 2015; 74: 115-124. doi:10.1017/S0029665114001578

(42) **POWE CE, EVANS MK, WENGER J, ZONDERMAN AB, BERG AH, NALLS M, TAMEZ H, ZHANG D, BHAN I, KARUMANCHI A, POWE NR, THADHANI R.** Vitamin D–Binding Protein and Vitamin D Status of Black Americans and White Americans. N Engl J Med. 2013; 369: 1991-2000. doi:10.1056/NEJMoa1306357

(43) **RAZZAQUE MS.** Sunlight exposure: Do health benefits outweigh harm? J Steroid Biochem Mol Biol. 2018; 175: 44-48. doi:10.1016/j.jsbmb.2016.09.004

(44) **REJNMARK L, AVENELL A, MASUD T, ANDERSON F, MEYER HE, SANDERS KM, SALOVAARA K, COOPER C, SMITH HE, JACOBS ET, TORGERSON D, JACKSON RD, MANSON JE, BRIXEN K, MOSEKILDE L, ROBBINS JA, FRANCIS RM, ABRAHAMSEN B.** Vitamin D with calcium reduces mortality: patient level pooled analysis of 70,528 patients from eight major vitamin D trials. J Clin Endocrinol Metab. 2012; 97: 2670-2681. doi:10.1210/jc.2011-3328

(45) **RØNN SH, HARSLOF T, PEDERSEN SB, LANGDAHL BL.** Vitamin K2 (menaquinone-7) prevents age-related deterioration of trabecular bone microarchitecture at the tibia in postmenopausal women. Eur J Endocrinol. 2016; 175: 541-549. doi:10.1530/EJE-16-0498

(46) **SÁNCHEZ-MARTINEZ R, CASTILLO AI, STEINMEYER A, ARANDA A.** The retinoid X receptor ligand restores defective signalling by the vitamin D receptor. EMBO Rep. 2006; 7: 1030-1034. doi:10.1038/sj.embor.7400776

(47) **SANCHEZ-MARTINEZ R, ZAMBRANO A, CASTILLO AI, ARANDA A.** Vitamin D-dependent recruitment of corepressors to vitamin D/retinoid X receptor heterodimers. Mol Cell Biol. 2008; 28: 3817-3829. doi:10.1128/MCB.01909-07

(48) **SCHURGERS LJ, UITTO J, REUTELINGSPERGER CP.** Vitamin K-dependent carboxylation of matrix Gla-protein: a crucial switch to control ectopic mineralization. Trends Mol Med. 2013; 19: 217-226. doi:10.1016/j.molmed.2012.12.008

(49) **SINGH G, BONHAM AJ.** A predictive equation to guide vitamin D replacement dose in patients. Journal of the American Board of Family Medicine : JABFM. 2014; 27: 495-509. doi:10.3122/jabfm.2014.04.130306

(50) **SINHA A, HOLLINGSWORTH KG, BALL S, CHEETHAM T.** Improving the vitamin D status of vitamin D deficient adults is associated with improved mitochondrial oxidative function in skeletal muscle. J Clin Endocrinol Metab. 2013; 98: E509-E513. doi:10.1210/jc.2012-3592

(51) **UWITONZE AM, RAZZAQUE MS.** Role of Magnesium in Vitamin D Activation and Function. J Am Osteopath Assoc. 2018; 118: 181-189. doi:10.7556/jaoa.2018.037

(52) **VON ESSEN MR, KONGSBAK M, SCHJERLING P, OLGAARD K, ODUM N, GEISLER C.** Vitamin D controls T cell antigen receptor signaling and activation of human T cells. Nat Immunol. 2010; 11: 344-349. doi:10.1038/ni.1851

(53) **ZAREI A, MOROVAT A, JAVAID K, BROWN CP.** Vitamin D receptor expression in human bone tissue and dose-dependent activation in resorbing osteoclasts. Bone Res. 2016; 4: 16030. doi:10.1038/boneres.2016.30