VITAMIN D3 + K2

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VITAMIN D3 + K2

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VITAMIN D3 + K2
THE SCIENCE BEHIND

KEY POINTS

- Many athletes will be deficient in vitamin D in the winter months, with few athletes presenting with 125nmol/L which may be the optimum for muscle regeneration and immune function.
- Low vitamin D concentrations have been shown to impair muscle recovery, increase the chance of a URTI, increase the severity of a URTI and in severe cases can result in osetomalacia.
- Based on current evidence, supplementing daily as opposed to weekly, with vitamin D3 in the range of 2,000 IU/day appears to pose no harmful effects and is within both the European and American safe upper limits for daily intake [9, 43].
- Vitamin D3 should be used over the D2 form, as the latter has lower potency and its biological importance in humans is debated [44]. This strategy of D3 supplementation could be employed in climates where there is little sun exposure during winter months (October-March) or where climate, lifestyle and socio-economic differences prevent sun exposure, such as in the Middle East, where vitamin D deficiency is prevalent [45].

WHAT IS VITAMIN D AND HOW IS IT MADE?

Vitamin D is often termed as the 'sunshine vitamin' given that the majority of Vitamin D3 (cholecalciferol) is made in the skin via sunlight (specifically ultraviolet B radiation exposure). In fact, it could be argued that Vitamin D is not a vitamin given that it can be made in the body. However, given in the winter months it is not possible to synthesis vitamin D an alternate route of intake is essential. The synthesis of vitamin D starts when the absorbed radiation from the sun causes the cholesterol precursor, 7-dehydrocholesterol to form pre-vitamin D3 which is then converted to vitamin D3 [1]. The significance of solar vitamin D production is clear when we consider that countries with low sunlight exposure for many months of the year have populations with the lowest vitamin D concentrations [2]. It has been suggested that more than 80% of vitamin D synthesis comes via sunlight with less than 20% from dietary sources and therefore in the winter months when sunlight is limited it is little wonder that many people, including athletes have been shown to be clinically deficient in Vitamin D. Indeed, the average daily intake across the world is approximately 100-250 IU, which is less than the current RDA of 400 IU (UK) and 600 IU (North America).

Once in the circulation, vitamin D3 is bound to the vitamin D-binding protein (DBP) where it is transported to the liver to be converted to 25-hydroxyvitamin D (25[OH]D, also known as calcifediol) under the control of the enzyme CYP2R1 [3-5] and then further hydroxylated to the activin the kidney to the active form known as 1,25 dihydroxy vitamin D (1, 25[OH]2D, also known as calcitriol). It is the bioactive 1,25 dihydroxy vitamin D that is transported in the blood to target tissues [3] that express the vitamin D receptor (VDR) subsequently regulating gene transcription. Whilst the traditional role of vitamin D was in regulating bone health, in recent years many tissues of the human body have been shown to have VDR including skeletal muscle and immune cells highlighting the importance of this vitamin in a variety of biological functions. Indeed, it is now understood that aspects of innate and acquired immunity,

VITAMIN D3 + K2
THE SCIENCE BEHIND

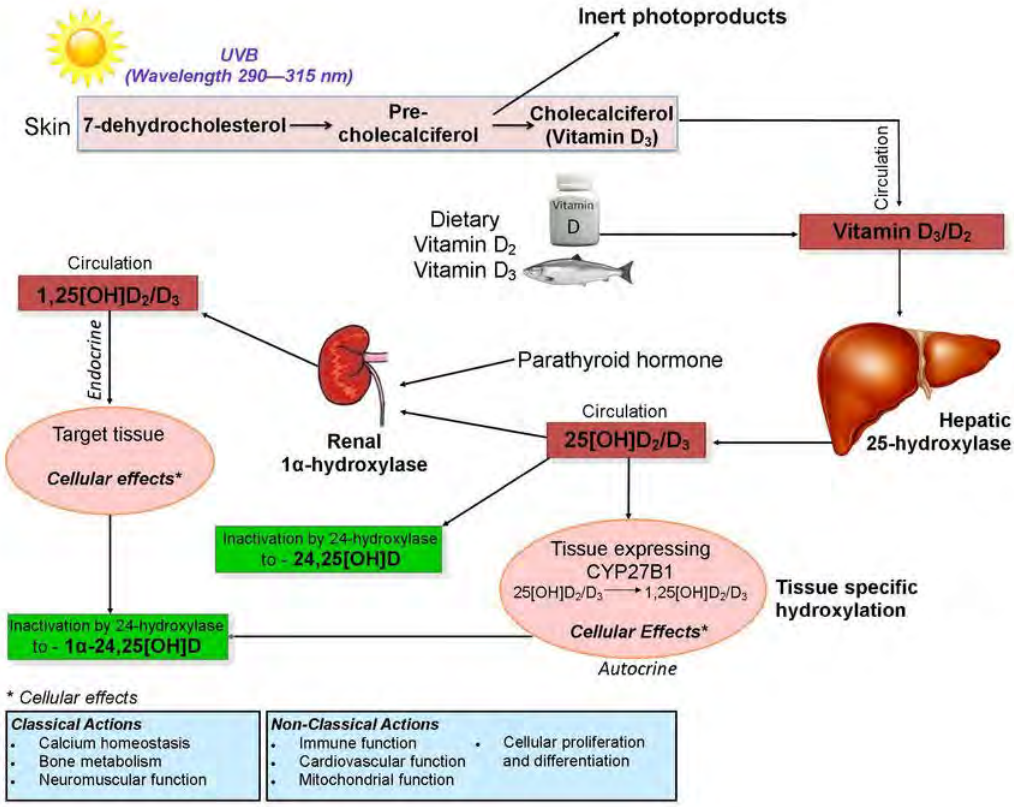

Figure 1: Vitamin D synthetic and metabolic pathways. Vitamin D obtained is from UVB stimulated photosynthetic reactions (approximately 80%) or dietary intake (approximately 20%). This is then transported in the circulation to the liver and kidneys where it is hydroxylated becoming 'active'. Through interaction with the vitamin D receptor, active vitamin D regulates many biological processes [Redrawn from 6].

cardiovascular health and biological processes within skeletal muscle are all regulated by vitamin D. A summary of the synthesis of vitamin D can been in figure 1 below.

WHAT IS VITAMIN D DEFICIENCY?

Despite this growing understanding of the importance of vitamin D, studies in both athletic and non-athletic populations consistently demonstrate that vitamin D deficiency is common owing to a sun shy lifestyle and poor dietary intakes of vitamin D [7]. In professional football players from the English premier leagues, it has also been shown that deficiencies occur in the winter months [8]. It should be stressed that there are not many foods (with the exception of fortified foods and supplements) that contain sufficient vitamin D to prevent deficiencies and therefore in winter months it is difficult to maintain a sufficient vitamin D status. This poses a unique problem for athletic populations as deficiency may go unnoticed but such deficiencies could contribute to sub-optimal immune function, poor bone health and potentially perturbed muscle function and regenerative capacity.

One of the sources of confusion when it comes to vitamin D is the establishment of consistent thresholds for the determination of vitamin D deficiency. Vitamin D status is typically categorised using the US Institute of Medicine classifications which can be seen in Table 1 [9], however many researchers believe that these are too conservative [10].

VITAMIN D3 + K2
THE SCIENCE BEHIND

Serum 25[OH]D	Status
< 12 nmol.L^{-1}	Severely deficient
12 – <30 nmol.L^{-1}	Deficient
30 – 50 nmol.L^{-1}	Inadequate
> 50 nmol.L^{-1}	Adequate
>100 – 250 nmol.L^{-1}	Suggested optimal [15]

Table 1: US Institute of Medicine (2011) vitamin D concentration classification and suggested optimal [15].

Whilst there is little argument that vitamin D concentrations below 50nmol/L are inadequate and should be corrected, there is growing evidence that greater than 100nmol/L may be beneficial for athletic performance, especially in terms of preventing winter infections [11, 12] and boosting recovery from muscle damaging exercise [13, 14]. Research from UK based athletic populations has shown that in the winter months the vast majority of athletes prevent with vitamin D less than 50nmol/L with very few athletes achieving >100nmol/L without specific vitamin D supplements [13].

HOW SHOULD WE MEASURE VITAMIN D AND WHAT SHOULD WE MEASURE?

Despite 1,25[OH]2D being the active metabolite, the measurement of serum 25[OH]D concentration provides the best estimate of vitamin D status [16, 17]. This is because 1,25[OH]2D has an extremely short half-live (4-6 hrs) and thus circulating 1,25[OH]2D concentrations provide limited information about vitamin D status. Moreover, if there is a vitamin D deficiency, parathyroid hormone increases and maintains 1,25[OH]2D levels so much so that it is only in severe deficiency that 1,25[OH]2D become low. There are many methods to assess 25(OH)D however studies have clearly shown that only mass spectrometry methods have the reliability required for the accurate assessment [18]. Whilst venous blood samples are routinely taken for clinical assessment, in recent years finger prick tests have been developed with the ones using mass spectrometry being proven to be a valid assessment method [19].

There is currently some interest in assessing bioavailable vitamin D concentrations (that is the fraction not bound to vitamin D binding protein and albumin) especially in darker skinned individuals [13, 20, 21]. This is because there appears to be a 'paradoxical relationship' between ethnicity and vitamin D concentration, that has largely been ignored, i.e. black athletes generally have the lowest vitamin D concentrations but the greatest bone mineral density (BMD) and reduced risk of fracture [22, 23]. Assays of bioavailable vitamin D, however, are not routinely available so for now the assessment of total 25(OH)D is the best although some caution should be exerted when interpreting these findings with darker skinned individuals.

WHAT ARE THE PHYSIOLOGICAL CONSEQUENCES OF VITAMIN D DEFICIENCIES?

There are a growing number of physiological roles of vitamin D, however from a sport and performance perspective the 3 major ones are:

- Bone Health
- Muscle function
- Immune health

VITAMIN D3 + K2
THE SCIENCE BEHIND

BONE HEALTH

The major function of vitamin D is calcium absorption and bone mineralisation [24] with the relationship between 25[OH]D deficiency and bone health being well described [25-31]. Indeed, the bone disease rickets (children) and osteomalacia (adults) is clearly associated with vitamin D deficiency. However, vitamin D deficiencies are not always associated with bone loss or fractures in athletes, a population where stress fractures are frequently observed [32]. This may be due to the osteogenic stimulus of exercise counteracting any marginal vitamin D deficiencies. From a bone perspective, it would appear that the key is to avoid clinical vitamin D deficiencies (less than 50nmol/L).

MUSCLE FUNCTION AND REMODELING

Given that many athletes are vitamin D deficient [8] and there is accumulating evidence associating vitamin D with skeletal muscle function it is no surprise than many athletes have now started to supplement with vitamin D. Studies assessing the effects of vitamin D on muscle function have generated conflicting results [33-36]. For example, Close et al, found improvement in 10-m sprint times and vertical jump height following supplementation with 5,000 IU/d D3 [37] as did Sinha et al. who demonstrated that supplementing severely deficient athletes (<6 ng/mL) with 20,000IU D3 on alternative days significantly elevated phosphocreatine recovery half-time (τ½ PCr) of the soleus muscle following activity, indicative of improved mitochondrial oxidative function [38]. However, other studies have shown no improvement in muscle function in vitamin D inadequate young active males [39]. It would appear that in terms of muscle function, problems are only observed when athletes present with very low vitamin D concentrations (<20nmol/L). It would therefore appear that in terms of muscle strength and function, vitamin D is not an ergogenic aid, rather, correcting deficiencies restores muscle function.

In contract to muscle strength, evidence does now exist to suggest that that maintaining serum 25[OH]D concentrations at around 75nmo/L may be beneficial for muscle recovery following damaging exercise. Supplementation of vitamin D to men improved muscle force recovery following a high-volume session of eccentric lower limb contractions. In the same study, muscle biopsies were taken to obtain myoblasts which were 'damaged' in vitro. These damaged myoblasts demonstrated improved muscle regeneration when incubated in higher concentrations of vitamin D suggesting that maintaining serum 25[OH]D, possibly at around 75nmol/L, may be beneficial for enhancing reparative processes and potentially for facilitating subsequent hypertrophy [40].

IMMUNE HEALTH

The maintenance of immune health, and specifically avoiding upper respiratory tract infections (URTI), is crucial for athletes and the general public alike given that even modest immune perturbations can reduce playing time, selection availability and disrupt training programs. Vitamin D has long been known to modulate immune health however the relationship with immune function and athletes is an emerging research discipline. Work from Mike Gleeson's laboratory in Loughborough has generated a growing evidence base suggesting that increasing vitamin D concentrations could reduce the chances of getting a URTI in a dose response manner [11, 12]. During a 16-week period of winter training athletes with the lowest vitamin D concentrations had the greatest risk of a URTI and if they did get one demonstrated the most serve symptoms with those >125nmol/L have the lowest risk [11]. It could therefore be argued that to maintain optimum immune function athletes should aim for a 25(OH)D concentration around 125nmol/L which will require supplements during the winter months.

VITAMIN D3 + K2
THE SCIENCE BEHIND

HOW SHOULD WE SUPPLEMENT VITAMIN D

Whilst the average daily intake across the world is approximately 100-250 IU, which is less than the current RDA of 400 IU (UK) and 600 IU (North America) it has been suggested that substantially greater doses are required when supplementing to correct deficiencies. In the literature, doses between 400-10,000iU per day are routinely given although it must be stressed that both EFSA and US IoM have set the safe upper limit at 4,000iU per day. We would therefore never recommend that doses above 4,000iU per day are given. If deficiencies are observed, studies have shown that 2,000iU are able to correct this with no danger of overdose or toxicity. Whilst some authors have suggested that the risk of overdose and toxicity is unlikely, research in athletes have suggested that a bolus dose of 70,000iU per week did decrease PTH which remained depressed 6 weeks after withdrawal of the supplementation [41]. Indeed, this may account for reports of reduced bone health in older individuals who had been given prolonged high dose vitamin D supplements [42]. Vitamin D3 should be given over D2 and a daily supplement has been proven to be more effective than weekly or monthly. Taken together, a moderate daily dose of vitamin D3 (2,000 IU per day) may be most appropriate if there is a need to supplement with vitamin D. Ideally a blood sample would be taken to diagnose a deficiency, however if this is not possible a moderate dose of 2,000 IU per day during the winter months could be appropriate.

We have established that Vitamin D is an essential micronutrient for athletes with emerging evidence suggesting that many athletes may be efficient in this vitamin (Owens, Allison and Close, 2018). Without an adequate supply of Vitamin D, the calcium that is consumed through the diet is not effectively absorbed and utilised by the body. However, recent studies are beginning to suggest that Vitamin D taken alone may not be as effective as when combined with another important vitamin, this being Vitamin K. The reason for this is that the proteins synthesised by Vitamin D need to be later activated by Vitamin K so Vitamin D in the absence of Vitamin K may be suboptimal

WHAT IS VITAMIN K?

Vitamin K is a fat-soluble vitamin essential for several physiological processes, most notably for blood coagulation (clotting) and bone health. The name "Vitamin K" originates from the German word "Koagulation," reflecting its critical role in blood clotting (Shearer, 1995). Vitamin K facilitates the carboxylation of specific proteins, enabling them to bind calcium, a process necessary for the activation of these proteins (Ferland, 2012). The most well-known function of Vitamin K is in synthesizing clotting factors, such as prothrombin, in the liver. Without adequate Vitamin K, these clotting factors remain inactive, which can lead to uncontrolled bleeding (Vermeer and Schurgers, 2000). Beyond its role in blood clotting, Vitamin K is also involved in bone metabolism and cardiovascular health (Booth et al., 2004; Booth, 2009). In the context of the interplay between Vitamin K and Vitamin D, Vitamin K is essential for activating proteins like osteocalcin, which facilitates the incorporation of calcium into the bone matrix. This process is critical for bone mineralization and strength. Without sufficient Vitamin K, even if Vitamin D enhances calcium absorption, the calcium may not be effectively integrated into bones, leading to potential deficiencies in bone density and strength. This synergy highlights the importance of both vitamins in maintaining skeletal health.

WHAT ARE THE DIFFERENT FORMS OF VITAMIN K?

Vitamin K exists in two primary forms:

Vitamin K1 (Phylloquinone): This form is synthesized by plants and algae and is predominantly found in green leafy vegetables, such as spinach, kale, and broccoli (Booth et al., 2004). The vast majority of Vitamin K1 (about 70-90%) is ingested from green leafy vegetables with the rest coming from some oils, liver and eggs.

VITAMIN D3 + K2
THE SCIENCE BEHIND

Phylloquinone is the main dietary source of Vitamin K and is directly involved in the coagulation process (Shearer, 1995). Upon ingestion, Vitamin K1 is absorbed in the small intestine and transported to the liver, where it participates in synthesizing clotting factors. The chances of Vitamin K1 deficiencies are rare in healthy adults, given that Vitamin K1 is commonly found in a variety of vegetables and the body efficiently recycles Vitamin K1 in a process known as the Vitamin K cycle (Vermeer and Schurgers, 2000). Moreover, only small amounts of Vitamin K1 are required to maintain normal blood clotting functions (Ferland, 2012), amounts readily obtained in most diets.

Vitamin K2 (Menaquinones): Vitamin K2 is a group of compounds thought to play a broader role in the body, particularly in bone and cardiovascular health by regulating calcium deposition (Vermeer and Schurgers, 2000). Unlike Vitamin K1 which primarily targets the liver, Vitamin K2 has a wider distribution in other tissues including bones and arteries (Booth et al., 2004). Menaquinones are found in fermented foods (like natto, a fermented soybean product, and fermented yogurts), animal products (such as liver and eggs), and are also produced by gut bacteria (Plaza & Lamson, 2005). The different menaquinones are denoted as MK-4, MK-7 depending on the length of the side chain. Up to half of our Vitamin K2 requirements are met by its production from gut bacteria, although this does require a 'healthy' gut microbiome which can be lacking in both athletes and the public alike. MK-4 cannot be formed by gut bacteria (Suttie, 1995). Given that there are growing concerns about poor gut health and many Western diets do not contain fermented foods, questions have been raised regarding potential Vitamin K2 deficiencies in many societies (Suttie, 1995; Zhang et al., 2024). Moreover, recent attention has focused on potential 'suboptimal' Vitamin K2 concentrations, which may not pose an immediate problem but could lead to poor bone and cardiovascular health over time. In 2009, following a review by the European Food Safety Authority (EFSA), Vitamin K2 was approved for use in European food and nutritional supplements (EFSA, 2009).

HOW SHOULD WE SUPPLEMENT VITAMIN D

Vitamin K and Vitamin D are both crucial for bone and cardiovascular health, and they interact in complex ways, particularly concerning calcium metabolism. Vitamin D is essential for calcium absorption from the intestine, as it increases calcium concentrations in the blood by enhancing calcium absorption from food (Holick, 2007). However, simply raising calcium concentrations without proper regulation may not be the optimal way to ensure calcium is delivered to the target tissue, i.e. bone(Shioi et al., 2020). This is where Vitamin K, particularly K2, plays a vital role. Vitamin K2 activates proteins in the bones (e.g., osteocalcin) and in blood vessels (e.g., matrix Gla-protein [MGP]) (Ferland, 2012). Osteocalcin helps deposit calcium into the bone matrix, enhancing bone strength, while MGP prevents calcium from depositing in the arteries, thus protecting cardiovascular health (Booth, 2009).

In essence, Vitamin D boosts calcium concentrations, while Vitamin K2 ensures that this calcium is properly utilized and directed to the right places (bones rather than arteries). Without sufficient Vitamin K2, the beneficial effects of vitamin D on bone health might be compromised, and the risk of vascular calcification might increase (Vermeer and Schurgers, 2000).

CONCLUSION AND RECOMMENDATIONS

Vitamin K is a vital nutrient, best known for its role in blood clotting and bone health. It comes in two main forms: Vitamin K1, which is involved in blood clotting, and Vitamin K2, which supports bone and cardiovascular health (Booth et al., 2004; Booth, 2009). The relationship between Vitamin K and Vitamin D centres around calcium metabolism, where vitamin D increases calcium absorption, and Vitamin K, especially K2, ensures that calcium is directed to bones and not to soft tissues, maintaining both bone integrity and cardiovascular.

NX

VITAMIN D3 + K2
THE SCIENCE BEHIND

While there is evidence supporting the synergistic relationship between Vitamin K2 and Vitamin D, it must be stressed that the research is not yet conclusive regarding the necessity of co-supplementation in all cases (Rosen, 2011). However, most studies show positive effects on bone density and cardiovascular health when both vitamins are taken together, but large-scale, long-term clinical trials are still needed to establish definitive guidelines.

There are now suggestions that the optimal Vitamin K requirements for the carboxylation of osteocalcin and Gla proteins are unlikely to be achieved from diet alone (Zhang et al., 2024). However, given the fact that Vitamin K is a fat-soluble vitamin, and it is relatively unstable, laboratory analysis of this vitamin has been suggested to be difficult to perform and this perhaps explains why it has not been the target of attention by athletes compared with Vitamin D. Given that Vitamin K2 has no known toxicity, even at higher doses, it makes sense that combined Vitamin D3 + K2 supplements are now being explored. While the optimal dose of Vitamin K2 is not well established, most studies use doses ranging from 75 to 200 µg of Vitamin K2. The MK-7 form of K2 is preferred due to its longer half-life (remaining in circulation for around 72 hours) and better bioavailability compared to MK-4 (eliminated after a few hours) (Suttie, 1995). In line with a food-first approach to performance nutrition (Close et al., 2022), it is important to consider increasing dietary intake of Vitamin K2-rich foods, including fermented foods, cheese, egg yolks, and chicken, as well as maintaining a healthy gut microbiota. Finally, if you are taking blood-thinning medications like warfarin, it is essential to consult with your healthcare provider before supplementing with Vitamin K2, as it may interfere with the medication's effectiveness (Shearer, 1995).

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NX

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THE SCIENCE BEHIND

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NX

VITAMIN D3 + K2
THE SCIENCE BEHIND

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