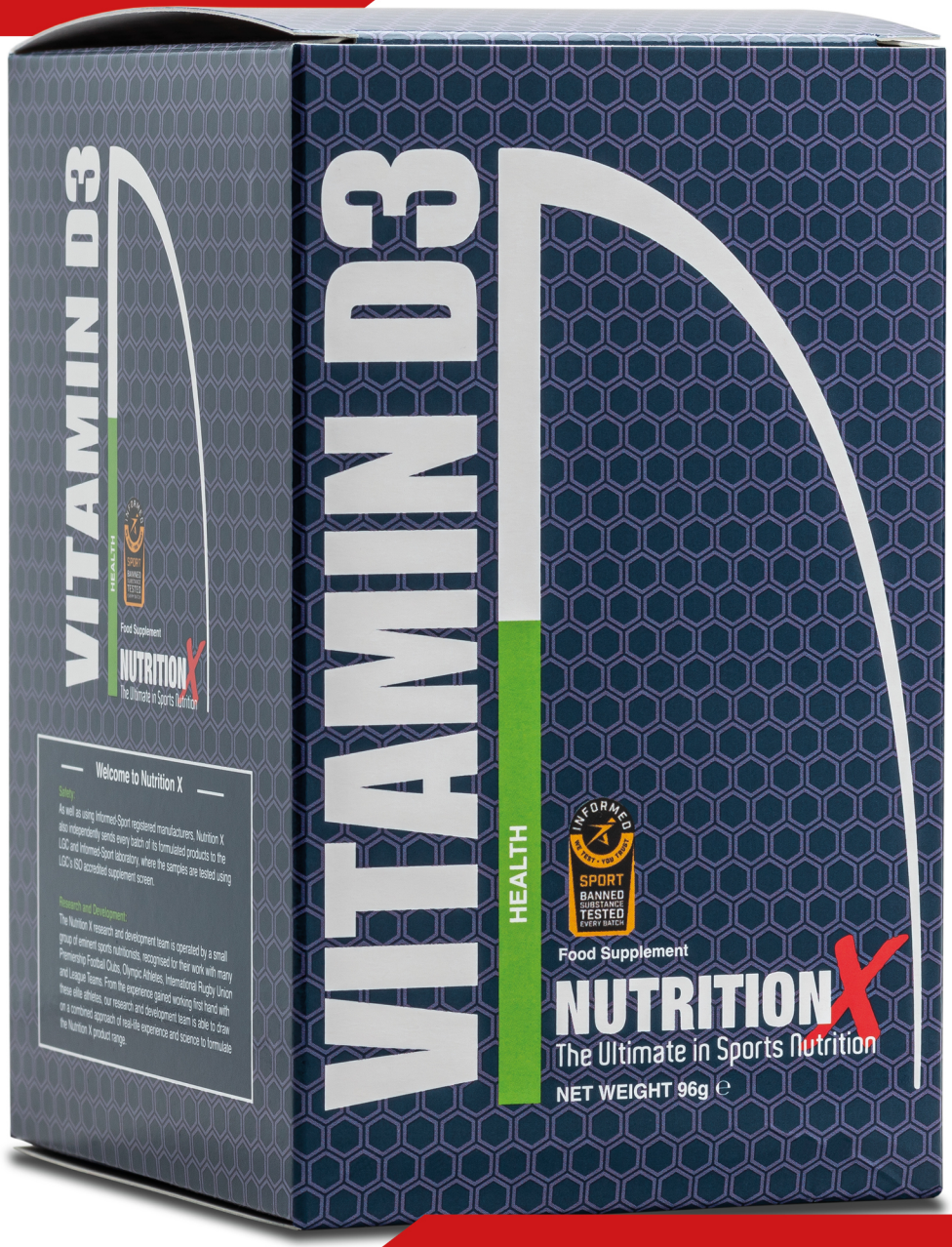
THE SCIENCE BEHIND



VITAMIN D3

Close, 2019

Vitamin D – The vitamin that perhaps should not be called a vitamin.

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 D_3 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 D_3 should be used over the D_2 form, as the latter has lower potency and its biological importance in humans is debated [44]. This strategy of D_3 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 D_3 (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 D_3 which is then converted to vitamin D_3 [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 D_3 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 dihydroxyvitamin D (1, $25[OH]_2D$, also known as calcitriol). It is the bioactive 1,25 dihydroxyvitamin 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, 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.

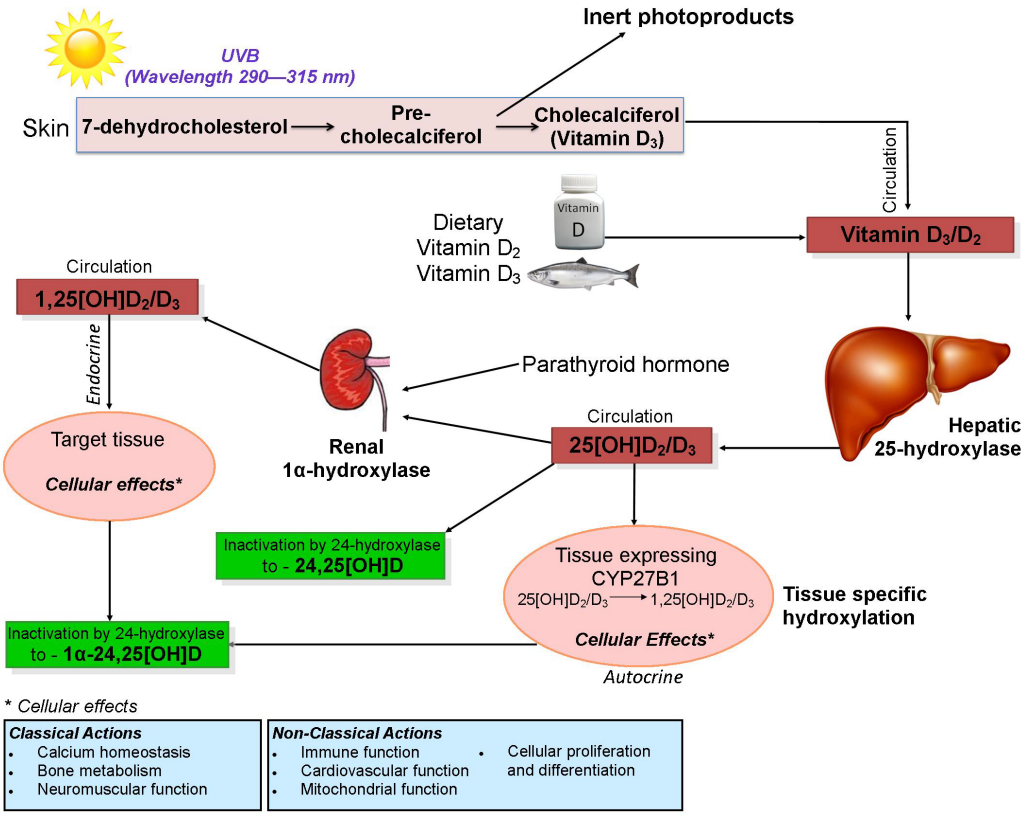


Figure 1. Vitamin D synthetic and metabolic pathways. Vitamin D obtained is from UVB stimulated photosynthetic reactions (approximately 80%) or dietary intake (approximately 20%). This is then transported in the circulation to the liver and kidneys where it is hydroxylated becoming 'active'. Through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

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]. 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].

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

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]

How should we measure vitamin D and what should we measure?

Despite 1,25[OH]$_2$D 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]$_2$D has an extremely short half-live (4-6 hrs) and thus circulating 1,25[OH]$_2$D concentrations provide limited information about vitamin D status. Moreover, if there is a vitamin D deficiency, parathyroid hormone increases and maintains 1,25[OH]$_2$D levels so much so that it is only in severe deficiency that 1,25[OH]$_2$D 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:

1. Bone Health
2. Muscle function
3. Immune health

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 D_3 [37] as did Sinha et al. who demonstrated that supplementing severely deficient athletes (<6 ng/mL) with 20,000IU D_3 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.

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 D_3 should be given over D_2 and a daily supplement has been proven to be more effective than weekly or monthly. Taken together, a moderate daily dose of vitamin D_3 (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.

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