VITAMIN D AND THE ATHLETE-PATIENT: STATE OF THE ART

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ABSTRACT

Vitamin D deficiency is common in athletes. The conventional measurement of vitamin D levels provides a general indicator of body stores. However, there are nuances in its interpretation as values of 25(OH)D do not correlate absolutely with the amount of 'bioavailable' vitamin to the cells. Vitamin D should be regarded as a hormone and influences between 5-10% of our total genome. Determining the precise effect of the vitamin, isolated from the actions of other co-factors, is not straightforward and restricts our complete understanding of all of its actions. Deficiency has harmful effects on not only bone and muscle but wider areas including immunity, respiratory and neurological activity. More caution should be applied regarding the ability of supra-normal vitamin D levels to elevate athletic performance. Hopefully, future research will shed more light on optimal levels of vitamin D and supplementation regimes, and improved understanding of its intra-cellular control of our genetic mechanisms and how extrinsic influences modify its activity.

INTRODUCTION

Much attention has been paid to the global problem of hypovitaminosis D. Over one billion people are estimated to be deficient. In sports science and medicine and orthopaedic surgery, the effect of hypovitaminosis D on athletes during training and performance, and with regard to avoidance of injury and recovery from treatments, including surgery, has been investigated.

This review will look at the sources of vitamin D, its actions and the sources of supplementation. It will investigate the implications for sporting performance, the evidence for hypovitaminosis D in causing injury, whether there are advantages in supplementation, and the potential implications for recovery from injury and surgery.

Most research on hypovitaminosis D has not been undertaken on the young, fit and healthy. Many publications are small cohort studies lacking the highest scientific vigour. They indicate potential associations rather than causation. The background to many injuries and illnesses are multifactorial. Hypovitaminosis D may be only one of many contributors.

Finally, one must consider what is meant by the term 'athlete'. Different sports vary in their cardiovascular, respiratory, musculoskeletal and neurological requirements. The elite athlete frequently displays extraordinary anatomy, physiology and genetic advantages. The 'weekend warrior' comes from a wide age-band with less imposing intrinsic credentials. However, all are at risk.

VITAMIN D STATUS IN THE ATHLETE AND PRE-OPERATIVE PATIENT

Many sports have been investigated with high numbers of athletes found to have hypovitaminosis D. Dark skin tones, participation in indoor sports, and living in higher latitudes are prominent risk factors. There are no large population studies directly comparing vitamin D levels in the athletes with more sedentary groups in the same society.

The prevalence of hypovitaminosis D in pre-operative orthopaedic patients mirrors the general population. Risk factors include trauma, sports-related surgery, the young, excessive

sunscreen use, males, and surgery during winter months [1,2]. These trends have been confirmed in shoulder [3] and foot and ankle surgical patients [2,4,5].

VITAMIN D PHYSIOLOGY

Conversion of Vitamin D

The processes for vitamin D conversion from its cutaneous and dietary precursors to the active metabolite and subsequent activity is shown in Figure 1.

25(OH)D, or calcidiol, is the inactive form of vitamin D and has a half-life of 21-30 days. A request for vitamin D estimation normally results in a measurement of this inactive metabolite. 25(OH)D represents a general indicator of body vitamin D stores. As a fat-soluble vitamin, it is stored in adipose tissue. Fluctuations in its levels are both an indicator of dietary intake and seasonal changes that affect cutaneous synthesis.

25(OH)D undergoes a second hydroxylation to produce the active metabolite, 1,25(OH)D, or calcitriol. The enzyme responsible is 1 α-hydroxylase (CYP27B1). CYP27B1 is found in many tissues. Its serum half-life is between 4-15 hours. 1,25(OH)D laboratory estimation is usually more involved and expensive. The less active metabolite 24,25(OH)D is formed in the kidneys.

Carriage of Vitamin D

Figure 2 shows how vitamin D is carried in the circulation.

The 'free hormone hypothesis' theorises that only unbound 1,25(OH)D can enter cells and exert influence but there is evidence that some tissues admit 1,25(OH)D bound to the vitamin D binding protein (VDBP). The levels and activities of VDBP influence vitamin D bioavailability to all tissues. This can alter the balance between free and bound vitamin D fractions. In such circumstances, the measurement of the total 25(OH)D3 levels may be misleading. 'Free' vitamin D measurements are not routinely available in clinical practice.

In black and Hispanic men, studies in both normal and athletic populations have reported high incidences of hypovitaminosis D [1,6]. However, the same groups have a lower risk of osteoporosis and fractures. The close relationship between vitamin D levels and bone mineral density (BMD) is clearer in lighter than darker skin tones [7]. The ability of black subjects to function at reduced vitamin D levels may be related to genetic variations in VDBP affecting the bioavailability of the vitamin [8].

Vitamin D receptors

Vitamin D receptors (VDRs) are found in most tissues and organs including the skin, placenta, bone, prostate, lung, breast, colon, pancreatic β cells, monocytes, lymphocytes, parathyroid glands, granuloma tissue [9]. $1,25(OH)D_3$ has been found to influence the activities of up to 5-10% of our total genome [10]. Figure 3 outlines the role of VDR activity. VDR expression declines with age and may play a part in the natural decline of sporting performance [11].

Calcidiol (25(OH)D), calcitriol (1,25(OH)D) and 'deficiency'

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The major circulating metabolite is the inactive form, 25(OH)D, and is measured in nmol/L (or ng/ml). The biologically active form, 1,25(OH)D, is present in much smaller amounts and is measured in pmol/L (or pg/ml). The relationship between the two is not precise. Conventional wisdom suggests that 25(OH)D levels have to fall to <20nmol/L to cause a significant reduction in 1,25(OH)D. Even at levels of 25(OH)D below 40nmol/L, Parathyroid hormone (PTH) levels rise and stimulates 1,25(OH)D production. This preserves intestinal calcium absorption [10].

An Italian study found 17% of patients had serum 25(OH)D$_3$ levels <25nmol/L - indicating severe deficiency. However, only 3% were severely deficient in 1,25(OH)D with levels <18pg/ml. It reported that low to moderate deficiencies of 25(OH)D were not necessarily associated with mineral homeostasis disorders but may have elevated PTH levels [12]. Severe deficiency was rarer for 1,25(OH)D and could be associated with normal levels of 25(OH)D. Severe deficiency of 1,25(OH)D is more likely to be associated with reduced levels of serum and urinary calcium.

This potential dissociation between the two metabolites should be considered when counselling patients. The relationship is multifactorial involving renal and parathyroid function and VDBP and albumin levels and activity.

25(OH)D may be regarded as a reasonable and relatively cheap primary screening tool of vitamin D reserves. However, suspected mineral homeostasis disorders in the athlete require a more detailed analysis. This should include measurements of serum 1,25(OH)D, the bioavailable 'free' concentrations, serum PTH, serum calcium and phosphorus, and urinary calcium. In the future, genotyping of important stages in the delivery of vitamin D to the cells, such as VDBP variations, will enhance our understanding of the 'vitamin D status' of our athletes.

VITAMIN D ACTIVITY

1,25(OH)D can be considered to have both endocrine activity and autocrine/paracrine activities [10]. The substrate should not be regarded as a vitamin but a secosteroid hormone.

The different pathways and location of various endocrine and autocrine/paracrine activity are shown in Figure 4.

WHAT IS A NORMAL VITAMIN D LEVEL?

There is no consensus for what constitutes normal serum vitamin D levels. Normal status should reflect the levels when the vitamin functions effectively at its target sites. This should include optimal benefits to bone, muscle, and all the other tissues and organs that host a VDR. The level should not excessively stimulate PTH causing secondary hyperparathyroidism. It is unlikely that one level of Vitamin D reflects all of these aims.

An athlete's vitamin D status can be regarded as deficient, insufficient or replete (normal). Figure 5 reflects how professional groups, researchers and various sporting organisations have defined reasonable levels to address issues of bone health, muscle function and immunity and infection defence [13-19].

VITAMIN D AND BONE HEALTH

Bone is a very active tissue. It grows during childhood and repairs following fractures. It undergoes constant structural repairs, has haemopoietic activity, and responds to the presence or absence of mechanical stimuli. Its health is dependent upon the interaction between multiple intrinsic and extrinsic factors, including those determining vitamin D status.

The knowledge that severe vitamin D deficiencies can produce rickets in children and osteomalacia in adults confirms vitamin D's importance for bone health. However, the link is not simple. Recent animal and human work suggest that vitamin D has both endocrine and autocrine/paracrine activities which influence bone health.

Rat experiments have examined the influence of restricting dietary vitamin D and calcium on bone structure and activity. Osteomalacia occurred when only both vitamin D and dietary calcium were severely restricted [20,21]. When 25(OH)D levels are <20nmol/L, 1,25(OH)D levels began to fall and hence calcium intestinal absorption. Severe reduction of 1,25(OH)D, by experimental ablation of the genes responsible for VDRs or 1-α hydroxylase enzymes (CYP27B1), diminishes intestinal absorption of calcium and phosphate. However, the development of osteomalacia can be overcome with high dietary calcium and phosphate [22].

Conversely, in animal studies, osteoporosis could occur when either vitamin D or dietary calcium were deficient individually [20,21]. Clinically, the risk of non-vertebral fractures does not fall until 25(OH)D levels are >80nmol/L [23]. In animal studies, maximum bone structure and strength occurred at 25(OH)D levels >80-100nmol/L combined with adequate calcium intake [24]. Rat and human serum vitamin D levels appear similar.

It appears that bone health is affected by more than the endocrine actions of vitamin D, since 25(OH)D levels >20nmol/L are likely to maintain endocrine activities. Vitamin D influence on bone does not appear to be VDR activation related – which occurs only at extremely high levels of 25(OH)D in experimental animals [25]. The effect appears mediated by the autocrine conversion of 25(OH)D to 1,25(OH)D within bone cells.

In vitro evidence suggests that osteoclast activity is reduced at 25(OH)D levels >80nmol/L and osteoblasts and osteocytes are stimulated to accelerate maturation and mineralisation by rising levels of 1,25(OH)D. Furthermore, increased dietary calcium appears to act as more than a structural asset for bone production. In animal studies, it upregulates 1α-hydroxylase activity within bone cells and encourages mineralisation. Theories on how increased levels of 1,25(OH)D affects osteoblast function are multiple. These include bone modelling signalling mechanisms, phosphate homeostasis, and enhancing the response to mechanical loading.

Does Vitamin D status affect peak bone mass in athletes?

Peak bone mass is achieved in late teens and early twenties shortly after peak height attainment [26,27]. After that bone mass plateaus and then gradually declines. This reduction accelerates for the female in the post-menopausal period. Failure to reach acceptable peak bone mass can have ramifications for the rest of an individual's life - particularly for fracture risk. These changes are depicted in Figure 6.

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The strength of evidence supporting the effect of lifestyle factors on bone mass has been considered [27]. Level A (strong evidence) factors included the effect of physical activity on bone mass and density, and adequate dietary calcium. Level B (moderate evidence) factors included the effect of exercise on bone structure, adequate vitamin D levels, and the inclusion of dietary dairy products. At the same moderate evidence level, contraceptive injections (e.g. Depo-Provera) have an adverse effect.

At lesser evidence levels, the beneficial effects of dietary fat, protein, fruit, vegetables and fibre have been examined as well as breast feeding. Similarly, the detrimental effects of carbonated drinks, caffeine, alcohol, cigarettes, oral contraceptives have been reported.

For females, another factor has both genetic and modifiable influences. The age of menarche can affect later peak bone mass. For many young females, the menarche can be delayed in part by certain physical activities. Long-distance runners, dancers and triathletes fall into this category. In females with a delayed menarche, low bone mineral density has been demonstrated even in the pre-pubertal period [28]. Longitudinal studies have demonstrated a close association between the age of menarche and the age at peak bone mineral content velocity (PBMCV) [29] and ultimate bone mass in young adults [30]. Late onset menarche is associated with weakened bone structure and reduced mechanical resistance. Not only does this increase fracture risk in adulthood but also in adolescence [31].

The advice to young athletes to sensibly supplement with vitamin D would appear reasonable. However, its influence on eventual peak bone mass may be only marginal. The adoption of the many lifestyle choices mentioned above should be combined to maximise bone strength. Athletes involved in repetitive high-impact activities do improve bone mineral density (BMD). This might help to offset naturally low 25(OH)D levels and partially explain the oft-observed lack of direct correlation between vitamin status and measurements of bone health. However, limbs that are not involved in such activities during recreation, e.g. upper limbs during running or low impact sports, place the athlete at similar risks of bone pathology at these sites as more sedentary patients.

Relationship between vitamin D and bone mineral density (BMD)

The relationship between 25(OH)D serum levels and the results of BMD measurements are not exact. Many patients will be found to have normal BMDs but inadequate vitamin D levels and vice versa. This is especially true for young athletes with darker skin tones [32,33].

Parathyroid Hormone (PTH), vitamin D metabolism and bone health

Low blood calcium stimulates the parathyroids to release PTH and induces secondary hyperparathyroidism. PTH increases the renal conversion of 25(OH)D to 1,25(OH)D. This in turn increases intestinal calcium and phosphate absorption. There is an age-related decrease in calcium absorption that may contribute to secondary hyperparathyroidism.

Low levels of 25(OH)D normally accompany low calcium levels and stimulate PTH secretion. Its mode of action is probably an autocrine activity. Falling 25(OH)D levels reduce the

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conversion to 1,25(OH)D in the parathyroid cells. The active vitamin within the cell regulates PTH secretion. As levels fall, increasing amounts of PTH are released [10].

Bone and kidneys have PTH receptors. If inadequate calcium is absorbed from the gut, 1,25(OH)D and PTH, together (acting via their receptors) release calcium from the bone stores and increase calcium reabsorption from the renal distal convoluted tubules.

The rationale for the use of vitamin D and calcium in protecting bone from injury is via its suppression of PTH levels. PTH (via its receptors) stimulates osteoclastic activity and releases calcium. This increases bone turnover and decreases bone mass.

Vitamin D levels needed to suppress PTH levels and minimise bone resorption are debated. Some suggest PTH levels plateau at 75nmol/L [34,35]. Others describe adequate suppression at 50nmol/L and bone metabolism markers are reported to stabilise at vitamin D levels >45 nmol/L [36]. It is not clear what the clinical significance is of higher serum PTH when the serum 25(OH)D levels are >50 nmol/litre in certain individuals with normal bone markers. Various explanations include age-related calcium absorption reduction, deteriorating renal function, and low calcium intake.

Other factors influence PTH levels including race, gender, weight, serum leptin levels, and serum sex hormone binding globulin. These may affect the varying range of serum 25(OH)D levels at which serum PTH is maximally suppressed. There may also be a form of receptor disease whereby tissues do not respond to PTH, which can lead to elevated levels of the hormone.

Functional hypoparathyroidism occurs with an inadequate PTH response to low vitamin D levels. Approximately 50% of people exhibit such a response. This can occur in all age groups [37]. Generally older patients tend to have higher levels of PTH for a similar Vitamin D serum level.

Supplementation may not be as effective in patients with functional hypoparathyroidism. However, several studies have indicated that patients with a low PTH response to low 25(OH) levels have higher BMDs. This may bestow a protective bone health effect [37,38].

ARE LOW VITAMIN D LEVELS ASSOCIATED WITH INCREASED INJURY RISK?

Publications have identified an association between fractures and hypovitaminosis D. This have been reported in mixed trauma groups [1,39] and specific locations such as hip [40-43], pelvis [44] and spine [45]. Links with trauma, [46-48] bone marrow oedema syndrome [49] and talar osteochondral lesions [50-52] have been described in the foot and ankle. However, one series demonstrated no difference in the spectrum of vitamin D deficiency in a foot and ankle trauma group compared to a pre-surgical non-trauma group sampled simultaneously in the United Kingdom [48].

Stress fractures are common in young, active individuals. Much research in this area has been undertaken in the military. The incidence in recruits has been estimated at between 0.2-5.2% in males and 1.6-30% for females. The economic burden can become great. Vitamin D

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deficiency has been associated with stress fractures in young, athletic adults in Finland, Israel, Britain and USA [6, 53-55].

Within tendons, vitamin D appears to be implicated in the balance affecting extra-cellular matrix components. Collagen degradation is aided by upregulating MMP (matrix metalloproteinases), which is counterbalanced by TIMP (tissue inhibitors of metalloproteinases) activity. Basic science research has indicated that vitamin D plays its role in downregulating MMP-9 [56,57]. An imbalance between MMPs and TIMPs has been associated with active tendinopathy and large tears of the rotator cuff [58-60].

DOES VITAMIN D SUPPLEMENTATION REDUCE INJURY RISK?

In the elderly, prevention of falls research and meta-analyses have produced varying results. Protocols have varied in terms of serum vitamin D starting levels, duration of supplementation, levels of serum blood vitamin D achieved, and the amount of vitamin D given. Benefits have varied from none [18,61] to fall reductions between 14%-22% [11,62-64]. A reasonable consensus from so many sources would be that the elderly should aim to maintain vitamin D levels in excess of 50-60nmol/L, which requires daily supplementation of 700-1000iu/day. Vitamin D and calcium together appear to be more effective at falls reduction than calcium alone [65].

A 21% reduction in stress fractures in female military recruits was reported during a 2-year period with calcium (2000mg) and vitamin D (800iu) supplementation[66]. Winter supplementation (2000iu/day) in a group of professional ballet dancers increased isometric strength and jump height and significantly reduced injuries [67].

Vitamin D, alone or in combination with calcium supplementation, has been reported to reduce fracture risks in the elderly [23,68]. Reduced muscle atrophy and hip fracture rates in post-stroke elderly females has been reported [69]. However, others found that supplementation with calcium and vitamin D improved hip bone density but did not reduce fracture risk significantly [70].

CAN VITAMIN D SUPPLEMENTATION INCREASE INJURY RISK?

Various studies have looked at the effect on fracture risk of intermittent high dose vitamin D supplementation in the elderly.

The administration of large one-off annual doses (500,000iu) in elderly females was reported to increase falls and hip fractures [71,72]. Others found a decrease in fractures with a four-monthly dosing-regime [73]. One report demonstrated a U-shaped curve effect of vitamin D supplementation. Maximum fall reduction occurred at levels of 80-95nmol/L and increased at levels beyond 100-112.5nmol/L [74]. The cause of increased falls with intermittent high doses and/or higher serum levels is unknown.

POTENTIAL EFFECTS OF HYPOVITAMINOSIS D ON SURGICAL RECOVERY

There is growing evidence that hypovitaminosis D adversely effects post-operative recovery for a wide range of orthopaedic procedures. However, published work has not concentrated on the athletic population.

Recovery delays from anterior cruciate ligament reconstruction has been reported [75]. Patients with 25(OH)D levels <50nmol/L had inferior outcomes 1-year after ankle fracture fixation [76]. Bone healing after foot and ankle fusions is worse at low vitamin levels [77,78].

Patients undergoing spinal surgery have a high prevalence of hypovitaminosis D [79] and have higher levels of pre- and post-operative pain, pedicle screw loosening, and revision rates. Fusion rates also appear to be lower [80-82].

For lower limb arthroplasty patients, low levels have been associated with longer in-patient stays [83,84], more post-operative pain [85], worse outcomes at 3-months [86] and 8-years [84] and increased risk of periprosthetic joint infection [87]. Moreover, vitamin D levels have been observed to fall following such surgery [88].

Altered MMP/TIMP balance has been associated with failure of shoulder rotator cuff tears, which vitamin D may influence [89]. Animal models have demonstrated impaired healing of rotator cuff tears in rats fed a vitamin D deficient diet [90].

For surgery in general, a systematic review reported that 26 out of 31 articles identified statistically significant and clinically important post-operative adverse outcomes associated with hypovitaminosis D. These included both surgical site and hospital-acquired infections, organ graft failure, myocardial infarction incidence, increased cancer risk post-organ transplantation, ICU stay, hospital in-patient stay and any cause one-year mortality after surgery [91]. Pre-surgical vitamin D status is the more relevant predictor of long-term outcomes compared to post-surgical vitamin D status, and minimal benefits are derived from supplementation in the peri- or post-operative period [92,93].

WHAT EFFECT MIGHT HYPOVITAMINOSIS D HAVE ON ATHLETIC PERFORMANCE?

Do low levels of Vitamin D impact on athletic performance? The evidence is mixed. Reduction in athletic performance in winter months and the benefits of exposure to UVB radiation have long been acknowledged.

Winter supplementation for dancers improved muscle strength and reduced injury [67]. A direct correlation between vitamin D levels and muscle power, force, velocity and jump height in 12-14-year old girls [94] and low vitamin D levels adversely affecting bone mass and turnover, and muscle strength in adolescent girls have been reported [95].

However, it could not be demonstrated that high doses of supplementation influenced physical performance over a 12-week period [96] and that 25(OH)D levels were not a predictor of athletic performance in adolescents [97].

Bone and Joint Health

Aspects of vitamin D status on bone health were explored earlier in this article. However, does it influence fracture healing? Animal studies have indicated benefits from vitamin D supplementation. With vitamin D's acknowledged role in bone health, its ability to influence cell differentiation and neuromuscular function, its role in inflammation and findings suggesting that deficiency is associated with re-fracture and delayed bone healing, it seems reasonable to conclude that maintaining vitamin D levels will help fracture healing. A systematic review of 114 papers in human fracture healing concluded that vitamin D appeared to have a role, but the precise mechanism was not clear [98].

Does the maintenance of vitamin D levels influence the later development of osteoarthritis in athletes? A systematic review found no link between vitamin D and hip or hand osteoarthritis but some evidence within the knee joint [99]. The need for RCTs to establish if supplementation can slow knee OA progression is required.

High BMI

High BMI levels are seen in certain sports. Obesity is associated with hypovitaminosis D and elevated PTH levels. Higher body mass index (BMI) individuals might spend less time exposed to ultraviolet B rays (UVB). Vitamin D is a fat-soluble vitamin stored within adipose tissues which reduce its bioavailability. Raised BMI is associated with a reduced response to UVB exposure and vitamin D oral supplementation. Both cutaneous and oral sources are sequestrated in large fat reservoirs. This needs to be considered when advising on supplementation.

Obesity is a chronic, low-grade inflammatory state. The tissues produce adipokines and macrophages that are proinflammatory. These proteins levels are influenced by BMI and vitamin D status. Hypovitaminosis D raises blood levels of such adipokines, e.g. TNF-α, CRP and IL-6. It appears that vitamin D acts as an anti-inflammatory and immuno-regulator.

Skeletal Muscle

The effect of vitamin D deficiency on skeletal muscle is well documented. Osteomalacia is associated with a marked proximal myopathy. Skeletal muscle biopsies reveal predominantly Type II muscle fibre change with atrophy, fat infiltration and fibrosis – an effect that can be reversed with vitamin D and calcium supplementation.

Vitamin D promotes skeletal activity in several ways. VDR activity promotes protein production. Additionally, it exerts its influence through signalling cascades promoting cell proliferation and differentiation [9(11)]. It regulates intracellular phosphate levels in muscle cells. In animal studies, vitamin D deficiency associated with hypocalcaemia did not produce muscle weakness, whereas hypovitaminosis D and hypophosphatemia caused profound but reversible changes [100].

Most research in this area has concentrated upon the elderly with regards to falls. Many elderly people develop progressive motor deficiencies that may be responsive to the positive

effects of supplementation. Indeed, VDR expression in muscle decreases with age contributing to a decline in sporting performance.

What relevance might this have to athletes training to develop adaptive responses to promote repair and remodelling of muscle following purposeful damaging eccentric exercise?

Younger athletes would be expected to have stronger muscle function with less margin for improvement. However, elevating vitamin D levels to greater than 75nmol/L has been shown to enhance recovery, remodelling and adaptation following intense exercise [101]. Supplementing with both vitamin D and calcium can increase type IIA (fast twitch) muscle fibres [102] and 1,25(OH)D is important in muscle recruitment by directing appropriate precursor cell differentiation [101].

Immune Response, Inflammation and Infection

Athletes often develop chronic fatigue. Additionally, they are prone to recurrent infections. Careful investigation frequently reveals underlying conditions, including deficient humoral immunity, allergies and asthma.

The VDR is found in cells involved in the immune response including T- and B-lymphocytes, monocytes, macrophages and neutrophils. Not only will these cells respond to circulating levels of vitamin D but are also capable of synthesizing 1,25(OH)D themselves. As such vitamin D exerts an autocrine action within such cells. Vitamin D can affect both the adaptive and innate immune response and deficiency can be associated with increased infection risk and the development of auto-immune disorders [103]. The ability of Vitamin D to coordinate the innate and adaptive arms of immunity has been found to be important in fighting diseases such as tuberculosis.

Vitamin D aids antimicrobial activity and VDBP helps Vitamin D bioavailability in addition to its own separate supportive cellular-level roles. A single, large dose of vitamin D has been shown to improve innate immunity [104]. Its effect upon the respiratory system will be discussed in the next section.

A link has been established between low vitamin D levels and the elevated biomarkers of inflammation found in runners [105]. The implications are not clear. TNF-α acts as a trigger for tissue repair and regeneration but is hypothesized to play a part in over-training syndrome, injury risk and immune suppression.

Pulmonary Health

Adequate vitamin D and VDBP levels are required for healthy pulmonary function. Various respiratory diseases have been associated with hypovitaminosis D including asthma, infection and chronic obstructive pulmonary disease (COPD). College athletes with low vitamin D levels are more likely to develop acute upper respiratory infections [106].

Maintaining winter vitamin D levels greater than 95nmol/L is reported to protect against viral infections. Below 95 nmol/L, the risk of developing upper respiratory tract infections (URTIs) doubled [107]. Others have reported that maintaining levels at greater than 75nmol/L in athletes

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prevents URTIs and enhances immunity [108], supplementation at 4000iu/day reduced RTI in high risk patients [109] and maintaining adequate vitamin D levels reduces the prevalence of Influenza A [110]. There is some early evidence that low vitamin D levels might be associated with greater mortality from COVID-19 [111].

Athletes have a higher incidence of asthma and allergic rhinitis than the normal population. Low levels of Vitamin D are associated with increased levels of eosinophils and IgE as well as an increase in hospital admissions and increased severity of asthma in both adults and children [108]. Screening susceptible athletes and supplementing with Vitamin D may reduce asthma exacerbations and secondary URTIs.

Thyroid disease

Both under- and over-activity of the thyroid can affect athletic performance. Associations between low vitamin D status and thyroid disease have been reported, particularly in the area of auto-immune diseases such as Hashimoto's thyroiditis. However, any causal relationship remains unresolved.

Diabetes Mellitus

Improved monitoring and control of diabetes has allowed sufferers to increasingly engage in sport – even at the highest level. Studies have shown that patients recently diagnosed with type 1 diabetes have reduced level of vitamin D. However, regular doses of vitamin D from a young age appears to reduce the risk of developing type I diabetes. Moreover, maintaining adequate levels of vitamin D appears to improve glycaemic control and insulin sensitivity in type I and II diabetics and in normal individuals.

Low levels of 25(OH)D have been found to be independently associated with insulin sensitivity and beta-cell function in patients at risk of type 2 diabetes [112] and it has been shown that patients with 25(OH)D levels below 75nmol/L were five times more likely to develop type II diabetes [113]. Additionally, hypovitaminosis D has been shown to be a possible risk factor for developing diabetic foot ulcers within the diabetic population [114,115].

Cardiovascular

As a result of intense athletic training (particularly in those sports requiring intense amounts of running), the cardiovascular system can undergo profound adaptive change that allows improved performance. These changes involve both electrophysiological and structural change. Indeed, the hypertrophic and ECG changes of the athletic heart can mimic pathology rather than evidence of a superbly adapted organ.

Whilst large studies on the effects of low vitamin D levels on cardiovascular disease have been published and those findings remain debated, the effects of variations in vitamin D status upon the athletic heart remains less well-researched.

Animal and human studies have demonstrated adverse effects on cardiac structure and function with vitamin D deficiency in the general population. Reduced hypertrophic changes

have been observed in athlete's hearts following training when vitamin D stores have been depleted [116,117].

Neurological disorders and pain perception

Athletes require highly developed neurological conditioning including balance, coordination and reflex responses. Additionally, many require an ability to tolerate pain without detriment to performance.

1,25(OH)D has an important role in both the central and peripheral nervous systems and is active in brain development and function. It is involved in myelin formation and differentiation, axonal distribution and homogeneity of peripheral nerves, and neuronal stem cell and myogenic differentiation. Vitamin D has been linked to several neurological disorders although its precise role requires further research [118,119]. In animal studies, mice deficient in VDR had decreased balance (vestibular) function [120].

93% of patients presenting with resistant non-specific musculoskeletal pain had Vitamin D levels below 50nmol/L [121]. They reported that young women were most at risk of delayed or misdiagnosis. Pain may be a strong feature of rickets osteomalacia and vitamin D induced myopathy [122].

Fatigue, Anxiety, Depression and Suicide

Most athletes will experience bouts of fatigue and anxiety during intense training and competition. At times, particularly during periods of prolonged recovery from injury, some will become depressed.

A direct link has been described between elderly subjects and fatigue as defined by reduced energy levels, muscle strength and cognitive activity [123].

The relationship between anxiety, depression, suicide and low vitamin D levels has been extensively investigated. Some researchers have found a positive correlation between depression and low vitamin D levels [124-126].

In a large Danish cohort, no link could be found between anxiety, depression and low vitamin levels [127]. US military personnel with vitamin D levels below 40nmol/L were reported to have an increased risk of suicide [128]. A possible association between seasonal affective disorder and low vitamin D has been reported [129].

VITAMIN D SUPPLEMENTATION

The decision to advise any athlete to supplement with vitamin D should be carefully considered. Is the vitamin D being prescribed to elevate serum levels to 'normal' range? Alternatively, is it being given to boost levels from adequate to supra-normal in the belief that such status prefers some form of ergogenic (performance enhancing) aid to the athlete? Figure 7 outlines the management pathway.

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Dietary Sources of Vitamin D

<u>Vitamin D can be found in a range of dietary products. These include oily fish, such as salmon, tuna, sardines, herring, and mackerel, and egg yolks, cod liver oil and cheeses. Some foods are fortified with vitamin D including breakfast cereals, certain dairy products, orange juice and soy milk.</u>

How much Vitamin D should the athlete take?

Various sports have published their supplementing algorithms. It should be recognised that within each regime, individuals' responses to similar dosage can vary greatly. Inevitably such tables are based on expert opinion rather than irrefutable objective data. A suggested scheme for supplementation is shown in Figure 8.

The main decision is whether to start with a loading regime or commence immediately with a maintenance dose. The decision should be based upon the initial vitamin D levels, evidence for adverse effects from the deficiency, the speed with which adequate vitamin D levels need to be reached, and the presence of any medical co-morbidities that warrant a cautious elevation of levels.

If a 300,000iu bolus is given with no follow up supplementation, it will last about three months assuming normal metabolic activity. It is advised to re-estimate blood levels at this stage and then administer a maintenance dose. It has been reported that 2-monthly boluses of 100,000iu will maintain levels above 75nmol/L in subjects with moderate baseline levels (50-75nmol/L). A maximum response at 7 days was noted. Younger patients had a more positive initial response and a sharper decline. Potential reasons for a more blunted response with age were a greater BMI and a lower hepatic 25-hydroxylase capacity [130].

What type of Vitamin D should the athlete take?

Cholecalciferol (D3) is preferable to ergocalciferol (D2) [19]. It is reported that vitamin D2 is much less effective than D3 in achieving desired serum levels [131].

Vitamin D alone or combined with calcium supplements?

The recommended daily allowance (RDA) for calcium is 1300mg for adolescents and between 1000-1200mg for adults. Once daily intake regularly exceeds 2000mg, the risks of harm increase [17], including cardiovascular disease and an increase in renal calculi. Calcium addition to vitamin D supplementation appears to improve longevity [132] and decrease in fracture risk in the elderly has been reported [133].

Monitoring of Vitamin D levels in the Athlete

When to measure an athlete's vitamin D blood levels depends upon whether it is for screening purposes or to monitor the response to supplementation.

Athletes advised to embark upon vitamin D supplementation should have their serum levels measured prior to commencement.

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For a patient taking the same daily or weekly dosage, an enhanced steady state of serum vitamin D levels will be obtained between 3 and 6 months. Therefore, under normal circumstances, repeat testing is not necessary before this period [18].

There are circumstances when an earlier repeat analysis might be deemed necessary. This would include a high initial loading dose or symptoms suggestive of vitamin D toxicity. It allows the patient's initial response to be monitored and subsequent dosage adjusted accordingly. However, a change of between 31-40% between serial measurements needs to be recorded to confirm that the observed difference is more than a combination of analytical and natural biological variability [134].

All clinicians prescribing vitamin D supplementation should be aware that it can unmask previously undiagnosed primary hyperparathyroidism (PHPT) – particularly if taken with calcium supplementation. PHPT is present in about 0.01% of the population. If high PTH levels are noted with vitamin D depletion, the levels should fall with vitamin supplementation. If not, PHPT should be suspected. While vitamin D repletion (in the presence of PHPT) helps bone mass restoration, it can increase the risk of hypercalcaemia.

Vitamin D Toxicity

Normal cutaneous vitamin D synthesis is self-regulating with increased melanin synthesis being one regulatory mechanism. However, excessive oral intake can in rare circumstances lead to toxicity. Serious consequences are mediated via hypercalcaemia leading to cardiac, renal and soft-tissue damage. Symptoms might include varying symptoms of malaise, abdominal pain, confusion, constipation, itching, weakness, thirst, fever, and chills. Other complications occur via increased urinary excretion of calcium.

Hypercalcaemia does not usually occur until vitamin D levels approach 250nmol/L [135]. However, some authorities caution on serum levels greater than 180nmol/L [18].

A daily dose of ≤10,000iu/day in the short-term is not associated with toxicity. Above these dosages, the duration of supplementation is important. In general, dosages of >50,000iu for longer than one-month risks hypercalcaemia[18].

Long-term intake of 4000iu/day has been advised as safe for most adults and children over 11 years of age, including pregnant and lactating women [18]. However, advice for people with co-morbidities predisposing to hypercalcaemia should be more restricted.

The body attempts to control high doses of vitamin D by converting more substrate to 24,25(OH)D, which adversely effects 1,25(OH)D signalling and reduces 25(OH)D conversion to 1,25(OH)D. One study found that after stopping high dose supplementation in athletes (70,000iu/week), levels of 24,25(OH)D levels remained elevated after 25(OH)D and 1,25(OH)D levels began to fall [136]. This might have a counterproductive effect on vitamin D activity and is one potential explanation of increased falls and fractures in the elderly after high dose supplementation.

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CONCLUSIONS

The need for vitamin D throughout the body is well-established. Equally the presence of hypovitaminosis D in many athletes is acknowledged. Its importance and ubiquity require it to be considered a hormone rather than a vitamin. However, it functions in part of a multifactorial milieu that affects such elements as bone and muscle function, immunity, inflammation and respiratory function, which are so vital for athletic performance, protection from injury and disability, and recovery from bone and soft-tissue damage. Consequently, the exact relationship between vitamin D and elements like bone density and muscle strength is hard to isolate. The advisability of maintaining vitamin D levels at 75-100nmol/L for optimal functioning during normal life and sport seems obvious. However, the evidence for maintaining vitamin D levels at supra-normal levels (i.e. >100-125nmol/L) to boost athletic performance is less clear.

Future research should concentrate on understanding how the amounts of 'bioavailable vitamin D' can be optimised, improving our knowledge on the autocrine and paracrine activities of the vitamin, and how genetic and epigenetic factors like training, ageing and diet might alter vitamin activity.

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<u>Figures</u>

Figure 1. Calcium homeostasis and Vitamin D conversion

Figure 2. Vitamin D carriage in circulation

Figure 3. The importance of VDR in vitamin D activity

Figure 4. Endocrine and Autocrine/Paracrine activity of vitamin D

Figure 5. What is a normal vitamin D level?

Figure 6. Peak bone mass and athletes

Figure 7: Vitamin D deficiency management

Figure 8. Vitamin D supplementation regime for the athlete
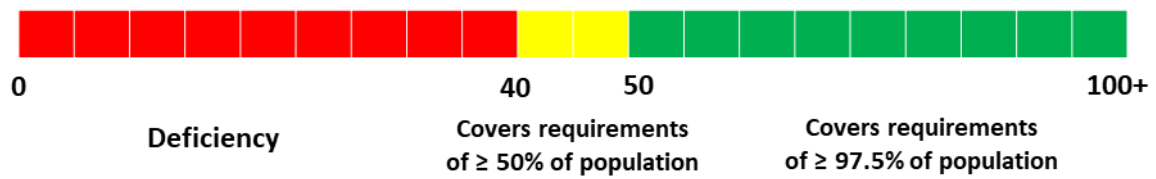
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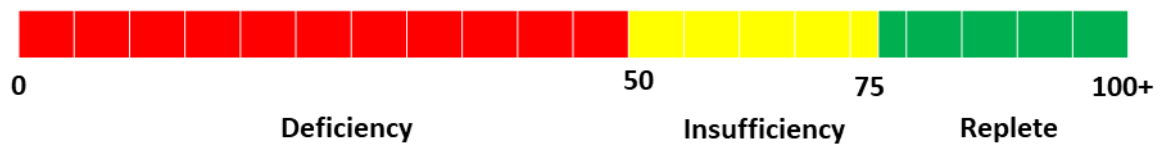# Box 2: Vitamin D levels (nmol/L) defined for assessment in general population

National Osteoporosis Society (UK) [19]

0	25	50
Deficiency	Insufficiency	Replete

Institute of Medicine (USA) [18]

0	40	50	100+
Deficiency	Covers requirements of ≥ 50% of population	Covers requirements of ≥ 97.5% of population	

Endocrine Society (USA) [17]

0	50	75	100+
Deficiency	Insufficiency	Replete

Box 3: What effect might hypovitaminosis D have on athletic performance?

- Adverse effect on bone health, including fracture healing
- Adverse effect on skeletal muscle function
- High BMI may effect vitamin D bioavailability
- Increased risk of infections
- Increased risk of immune disorders and development of autoimmune diseases
- Effect upon vital organs influencing athletic conditioning and performance:
  - Pulmonary
  - Cardiovascular
- Adverse effect upon diabetic control
- Increased risk of neurological disorders and altered pain perception
- Adverse psychological effects upon performance

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Box 4: FAQs about Vitamin D supplementation

Question	Advice
What type of vitamin D should the athlete take?	• **Cholecalciferol (D3) is preferable** to ergocalciferol (D2) [19] • Vitamin D3 is more effective than D2 in achieving desired serum levels [131]
Oral or intramuscular (im) vitamin D supplementation?	• **Both routes are effective** [137,138] • im route can lead to unpredictable release from injection site • Serum levels rise quicker with oral administration but by 3/12 response is similar [140] • Overall, **oral supplementation is preferable** in the athletic population unless there are any malabsorption issues
Where should an athlete source vitamin D supplements?	• Athletes subject to drug testing should only source supplements from manufacturers known to **comply with anti-doping agency testing regulations**
Should the athlete take a daily or intermittent dose of vitamin D?	• **Little difference in effectiveness** for vitamin D taken daily or in larger, less frequent doses [140]
How quickly will serum levels rise after starting supplementation?	• **Variable and dependent upon a number of factors:** initial serum levels; sun exposure; normal dietary intake; time of year; age; BMI; skin type; co-morbidities; genetic profile • **"Rule of Thumb":** • Healthy individuals: 1000iu/day > serum levels rise by 25-30nmol/L in 3-4 months [19,141] • Severely deficient: may need doses in >1000iu/day to achieve adequate levels [134]
When should athletes be routinely screened?	• **No consensus** • If annual: same time of year preferable • If bi-annual: End of winter and end of summer will give best indicator of absolute values and annual variability
Where should values be assessed?	• **Considerable variability** between different commercially available assays [142] • Use same laboratory for repeat screening for continuity
Vitamin D alone or with calcium (1200mg)?	• Combination appears to confer better bone protection [20,21,22]

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Box 5: Recommended Daily Intake (RDI) of Vitamin D

Country	Advisory Body	Age Group	RDI
United Kingdom	SACN (2016) [143]	>4 year old	400iu (10 microgrammes)
USA	Institute of Medicine (2011)[18]	Children	400-600 iu
		Adults (<70 years)	600iu
		Elderly	800iu
	Endocrine Society (Holick, 2011)[5]	Children	400-1000iu
		All adults	1500-2000iu
Australia	Osteoporosis Australia (2012) [144]	Adults (<70 years)	600iu
		Elderly	800iu

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Box 6: Vitamin D screening of individual athletes

Outside of mass screening programmes within a sport, individuals might warrant testing at other times. This depend upon the identification of specific risk factors. These would include:

- Racial and ethnic risk factors, e.g. dark skin tones
- Reduced exposure to UVB and excessive use of sun creams
- Recurrent infections
- History of recurrent injuries
- Bone injury
- Prior to planned surgery
- Altered vitamin D and calcium dietary intake
- Malabsorption conditions
- High BMI
- Diabetes
- Features of RED-S syndrome including amenorrhoea, excessive fatigue, and eating disorders
- Family history of hypovitaminosis D
- Risk factors for hypervitaminosis D and hypercalcaemia
- History of renal stones

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Box 7. Major Pitfalls of Vitamin D Screening

- **Vitamin D levels vary within individuals throughout the year**
  - Annual screening programmes should take place at the same time of the year

- **Due to different methods of analysis, vitamin D levels may vary in different laboratories**

- **A vitamin D 'test' will usually measure only the inactive form, 25(OH)D**

- **The relationship between 25(OH)D, and the active form, 1,25(OH)D, is not precise**

- **Complete analysis of vitamin D status should include:**
  - serum 25(OH)D
  - serum 1,25(OH)D
  - the bioavailable 'free' concentration of vitamin D,
  - serum PTH,
  - serum calcium and phosphorus
  - urinary calcium

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