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Vitamin D Deficiency in Athletes

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The Effects of serum 25(OH)D and Vitamin D Supplementation on Athletic Populations

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Literature Review

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Background: Vitamin D status in the United States is a concern with over half of the population having insufficient serum 25(OH)D levels. Vitamin D is essential for musculoskeletal mechanisms, which could lead to potential clinical issues within athletic populations. Examining the effects of serum 25(OH)D and vitamin D supplementation on musculoskeletal health and sports performance could alter the clinical approach toward the athletic population.

Purpose: The purpose of this project is to: 1. evaluate the most current literature to determine, within the athletic population, the prevalence of insufficient serum 25(OH)D; 2. determine the potential effects of insufficient serum 25(OH)D on athletic performance, bone and muscular health; and 3. develop an appropriate protocol for vitamin D supplementation to be translated for clinical application and intervention.

Methods: The Academy of Nutrition and Dietetics Evidence Analysis Process was used as a basis of methodology in determining the methods used for developing this literature review. The following electronic databases were searched to identify original peer-reviewed articles: PubMed, Google Scholar, and Collegiate and Professional Sports Dietitians Association (CPSDA) Research Library. Search words and key terms used in the search included “vitamin D”, “25(OH)D”, “athletes”, “performance”, “muscle mass”, “bone health”, “ethnicity”, “supplementation”. Randomized- controlled trials, cohorts, cross sectional analysis as well as systematic reviews and meta-analysis studies using human subjects published between January 2008 and October 2018 were included. Quality rating was assigned to studies to determine their “weight” in providing evidence for the research purpose.

Results: A total of 14 research studies were included in this literature review. There were a total of seven bone health, six muscular health, and eight performance and supplementation articles that matched the search criteria. Of the six bone health studies, four produced positive results on the relationship between 25(OH)D levels and stress fractures, bone mineral density, and bone turnover markers. Of the six muscular health studies, five produced positive results on the relationship between 25(OH)D and muscle injury, strength and performance. Of the eight supplementation studies, six were found to have positive results of any dose of vitamin D treatment in increasing 25(OH)D levels. The remaining two studies suggested a low dose (daily 200-4000 IU) only maintained 25(OH)D levels rather than increasing. Vitamin D_3 was the form used in all studies with a vitamin D supplementation intervention.

Conclusion: This literature review provides evidence of a positive impact of adequate serum 25(OH)D levels on physical performance, bone and muscular health. Vitamin D supplementation may benefit those with adequate serum 25(OH)D levels, but provides more benefit to those who have insufficient or deficient serum 25(OH)D levels. Comparison of dose and daily versus weekly vitamin D supplementation benefits remain inconsistent. More research is necessary to determine the specific benefits of vitamin D supplementation and serum 25(OH)D levels, particularly regarding its effect on bone health.

Introduction

Of the United States population, 77% are considered vitamin D insufficient, defined as 25(OH)D levels are <30 ng/mL.[1] The high prevalence may be the result of decreased sunlight during the winter months, malabsorption, darker skin color or the decreased ability to synthesize vitamin D with age. Vitamin D aids in various functions including mineral regulation and metabolic pathways, T cell activation, decreased inflammatory cytokines (IL-6,IL-8), and calcium, phosphate, and iron transportation and absorption. Each of these functions is regulated by interacting with the vitamin D receptor (VDR).[2] The VDR is found in almost all body cells including immune, vascular, and smooth muscle cells. This explains why vitamin D plays an essential role for immune function, inflammatory response, bone and muscle health.

Vitamin D insufficiency in athletes is an increasing concern as it may place them at higher risk for injury and negatively impact physical performance. Approximately 56% of the athletic population has vitamin D insufficiency (<32 ng/mL), according to a systematic review of twenty-three studies.[3] Vitamin D status among athletes depends largely on geographical location and type of sports (indoor or outdoor). Risk factors for vitamin D deficiency include low dietary intake of vitamin D and limited ultraviolet (UV) exposure (sun) and/or absorption (such as dark skin pigmentation). Examining the effect of vitamin D may have on muscle strength, injury prevention and sports performance could alter the clinical approach toward the athletic population.

Outline

This review of literature will discuss:

a) Measures of Vitamin D
b) Differences in Ethnicity and Bioavailable Measures
c) Effect on Bone Health
d) Effect on Skeletal Muscle
e) Effect on Physical Performance
f) Effectiveness of Vitamin D Supplementation

Table 1. Review article inclusion and exclusion criteria

Inclusion Criteria	**Exclusion Criteria**
English Language	Animal Subject
Human Subject	In Vitro Study
Published between 2008-2018	Published before 2008
Sample Size >10	Sample Size <10
Original peer-reviewed, randomized controlled, cohort, systematic review, meta-analysis	

Measures of Vitamin D

The currently accepted biomarker of vitamin D status is a blood test to measure total circulating 25-hydroxyvitamin D (25(OH)D) molecules.[4] This measure is the most accurate indicator of vitamin D status because it takes account for UV exposure, dietary and supplemental intake, and has a long half life of approximately 3 weeks. It has shown to be a reliable marker that is used in a variety of inpatient and outpatient clinical settings to define vitamin D deficiency. The majority of circulating 25(OH)D is bound to a Vitamin D binding protein (DBP), which carries vitamin D in the blood and belongs to the albumin family. Circulating 25(OH)D bound to DBP extends its half-life even further by 15-35%.[5] Although, DBP is not typically measured, recent research suggests some advantages.[6] Individuals with low DBP also tend to have lower levels of total 25(OH)D related to the shorter half-life. In this case, bioavailable 25(OH)D (non-protein bound) levels may still be sufficient resulting in the absence of characteristics associated with insufficient vitamin D including hyperthyroidism, hypocalcemia or low bone mineral density (BMD). However, from a clinical perspective, bioavailable 25(OH)D would not reflect long-term overall status of vitamin D, which is why total 25(OH)D is used to define vitamin D status. Consequently, research suggests DBP levels should be considered when analyzing total 25(OH)D as a biomarker. Levels of parathyroid hormone (PTH) can be an additional marker of vitamin D deficiency once low levels of 25(OH)D have

been established.[4] PTH further assesses the severity of vitamin D insufficiency related to its role in calcium homeostasis and PTH secretion, with potential ramifications for bone health. Vitamin D is involved in regulating the amount of calcium in the blood, as serum calcium levels begin to drop PTH is released to increase calcium reabsorption from bone.

There is a lack of consensus criteria for vitamin D deficiency and insufficiency. There is also a lack of agreement for recommended daily IU vitamin D intake. The Endocrine Society's clinical guideline suggests 1,500 IU vitamin D daily is necessary to ensure a normal level of >30 ng/mL.[7] Deficiency is defined as <20 ng/mL and insufficiency as 21-29 ng/mL. On the other hand, the Vitamin D Council recommends maintaining serum levels of >50 ng/mL with intake of 5,000 IU daily and serum 25(OH)D of <40 ng/mL being defined as deficient.[8] The Institute of Medicine (IOM) suggests consumption of 600 IU of vitamin D daily to reach >20 ng/mL is generally considered sufficient for healthy individuals.[9] They also propose serum levels of 25(OH)D above 50 ng/mL have potential adverse effects. Certain individuals may require higher doses based on age, weight, and medical conditions such as malabsorption, digestive disorders and bariatric surgery.

Table 2. Summary of General Population Vitamin D Recommendations

	Endocrine Society	Institute of Medicine	Vitamin D Council
Adequate	30-100 ng/mL	20-60 ng/mL	40-150 ng/mL
Insufficient	21-29 ng/mL	13-20 ng/mL	31-39 ng/mL
Deficient	<20 ng/mL	<12 ng/mL	<30 ng/mL
Toxicity	>10,000 IU daily	>50 ng/mL >4,000 IU daily	>150 ng/mL
Daily Recommendation	1,500 IU	600 IU	5,000 IU
Treatment	50,000 IU weekly for 8 weeks		

Differences in Ethnicity and Bioavailable Measures

Those with increased skin pigmentation, such as Asians and black Americans are more often diagnosed with vitamin D deficiency than white Americans.[10] It has been suggested the increased melanin found in darker skin may slow vitamin D synthesis by two-thirds the rate of whites. A study involving 634 subjects found white females had the highest circulating 25(OH)D levels, while black males were the lowest with 70% considered deficient (<20 ng/mL).[10] This same study also reported lower levels of 25(OH)D with higher levels of PTH, although bone health was not assessed. A later cohort study by Powe and colleagues, including 2085 subjects reported similar findings, although it did not include Asians.[6] They also found lower levels of 25(OH)D in black Americans compared to white Americans, which was inversely associated with increased levels of PTH regardless of race and ethnicity. However, this study also assessed BMD, which was higher in blacks than whites. Although blacks had higher levels of PTH, they also had higher levels of BMD. The authors concluded BMD and 25(OH)D were not correlated in blacks, but they were positively correlated in whites. A separate study of 1,200 female Navy recruits also found that although black Americans had the lowest mean 25(OH)D concentrations, their stress fracture risk was not significantly affected.[11] These results raise an interesting clinical question as to whether circulating 25(OH)D affects calcium homeostasis and bone health in black Americans to the same extent it affects white Americans.

Further, lower levels of DBP have been observed in blacks. Interestingly, blacks are more likely to have a genetic single nucleotide polymorphism (SNP) of the DBP gene.[6] Deoxyribonucleic acid (DNA) is hereditary and stores important information that influences growth, function and development of all living organisms. SNPs occur in human genome and are variations in DNA between genes. This particular SNP results in lower levels of DBP and may explain the low levels of total 25(OH)D in individuals who carry this genetic polymorphism. This polymorphism could possibly mask vitamin D sufficiency.[6] These findings together suggest total 25(OH)D may not uniformly detect vitamin D deficiency from one ethnicity to another, and possibly from one individual to another, which needs to be considered when using total 25(OH)D as a biomarker in a clinical setting. However, total 25(OH)D remains the accepted biomarker for vitamin D status and is used within research studies.

A 2015 study involving 80 National Football League (NFL) players reported black athletes had significantly lower vitamin D levels than the white athletes. In fact, 100% of the athletes deficient in vitamin D (<20ng/mL) were black and 91% of the athletes insufficient in vitamin D (20-32 ng/mL) were black.[12] Among all NFL players in this study, 68.6% were either deficient or insufficient. A separate NFL study involving 214 athletes found that overall injury history among black players was inversely associated with lower vitamin D levels; however, the type of injury was not specified (muscular or skeletal).[13]

Effect on Bone Health

As mentioned earlier, vitamin D plays a vital role in bone health by regulating calcium homeostasis together with PTH. With a lack of 25(OH)D, calcium absorption is reduced contributing to low levels of serum calcium. To help restore calcium levels, PTH triggers the kidneys to increase the release of calcium from the bone and increase reabsorption of calcium from the kidneys. This vicious cycle of low 25(OH)D can lead to diminished BMD and overall bone health.[7] Both calcium and vitamin D play a central role in bone formation and resorption. Cohort studies in postmenopausal women indicate that risk of fracture increases by a factor of 1.4–2.6 for each standard deviation decrease in BMD.[14]

Osteoporosis is diagnosed with a T-score of -2.5 or lower low bone mass is defined as a T-score between -1 and -2.5, and normal bone mass between 1 and -1 .[15] A Z-score is recommended by the International Society of Clinical Densitometry to use with individuals under the age of 50, as it compares age and gender unlike T-Score. Athletes should have 10-15% higher BMD than non-athletes, especially athletes in high-impact weight-bearing sports such as basketball, running, and soccer.[16,17] The American College of Sports Medicine defines low BMD as a Z-Score between -1 and -2.[17] Athletes who actively participate in non-weight-bearing sports such as swimming, cycling and rowing have consistently shown to have lower BMD. However, the National Collegiate Athletic Association (NCAA) reports stress fracture incidence in runners has been as high as 15%. An athlete with low BMD is at higher risk for stress reactions, stress fractures and bone injuries. A stress reaction occurs prior to an actual stress fracture being present. Repeated stress on the bone results in the body's inability to

efficiently form new bone (ossification) causing weakening of the bone. This repeated activity without sufficient rest time for repair can cause a stress fracture to form. In addition to low-impact sport participation, stress fractures are commonly associated with sudden changes in activity intensity or frequency, low energy availability, amenorrhea, insufficient 25(OH)D levels, and low body mass index (BMI). Amenorrheic athletes have approximately 10% lower BMD, will lose 2-3% of their bone mass each year if left untreated, and have 2-4 times the increased risk for developing a stress fracture.[17] All of these factors should be evaluated and treated if an athlete presents with a bone injury or low BMD.

Maroon, et al[12] reported a significant correlation between low levels of 25(OH)D and NFL players who had experienced one or more bone fractures, when controlling for the number of years played. A cohort study of 124 subjects reported an inverse association between stress fractures and 25(OH)D at ≤40 ng/mL.[18] Further, a cohort study of 1,200 female Navy recruits reported those with 25(OH)D concentrations >40 ng/mL had half the risk of developing a stress fracture compared to those <20 ng/mL.[11] It should be noted, only stress fracture data incidence for the tibia and fibula was gathered because these are the most common sites of injury in military recruits. In contrast, a study of 279 NBA players, reported 73.5% were vitamin D insufficient (20-32ng/mL) and found no association between vitamin D level and fracture history.[19] However, the authors did not have access to any possible prior vitamin D supplementation.

Effects on Skeletal Muscle

Recent research suggests vitamin D may play a direct effect on skeletal muscle through the VDR in myocytes.[2,6,20] This mechanism occurs through two pathways including a genomic and membrane signaling pathway. Binding of vitamin D to VDR may influence muscle function, contraction, and cell proliferation/differentiation. Because of the direct binding effect, an individual deficient in vitamin D may experience more immediate negative effects on muscle tissue before the bone.[7]

A study of 214 football players in the NFL combine examined the association between the incidence of muscle injuries and 25(OH)D levels.[13] Lower extremity muscle strains and core

muscle injuries were inversely associated with lower 25(OH)D levels. More specifically, marginal levels of 25(OH)D had an increased risk of lower extremity strain, core muscle injury and hamstring injury by 1.86 and 3.61, respectively. Similar muscle injury findings were discovered while monitoring 25(OH)D over a six-months among 32 collegiate swimmers and divers.[21] The authors reported 77% of connective tissue and muscle injuries occurred after a noted decrease in 25(OH)D levels. Interestingly, no bone injuries were reported, although skeletal injuries are less common in non-weight bearing sports.

A cross sectional study of 419 men and women (20-76 years) explored the relationship between serum 25(OH)D and muscle strength.[22] A significant positive correlation between 25(OH)D levels and both upper and lower muscle strength was observed when controlling for age and gender. A separate meta-analysis review of seven trials included 310 male and female adults (18-40 years old) and examined the effects of vitamin D supplementation on muscle strength, by assessing leg press, squats, chest press, bench press, and grip strength.[23] Mean baseline 25(OH)D was 12.3 ng/mL among all subjects. Vitamin D was supplemented from 4,000 IU per day to 60,000 IU per week; however, 25(OH)D levels were not monitored throughout the trial. Regardless, vitamin D supplementation was positively associated with a significant increase in both upper and lower strength.

Vitamin D Supplementation and Physical Performance

Once vitamin D insufficiency or deficiency in an athlete is identified, an optimal dose to elicit potential benefits of supplementations needs to be determined. Vitamin D_3 supplements (compared with D_2) have been shown to have the greatest impact on increasing the concentration of serum 25(OH)D due to high binding affinity to DBP.[24] Debate remains regarding the required dose of vitamin D supplementation. This debate exists as it relates to varying daily dose and optimal levels set forth by the IOM, The Endocrine Society and Vitamin D Council.[6-8] Further, individuals may respond differently to the same dosing regimen, suggesting there may not be an all-inclusive protocol. Although a daily dose may provide more stable concentrations of circulating vitamin D, some clinical trials use a weekly dose rather than daily to fully validate compliance of subjects. Due to this inconsistency, vitamin D supplementation

widely varies in dose and frequency. Common supplementation ranges from 2,000-5,000 IU daily or 35,000-70,000 IU weekly.

In one study, 42 athletes received either 35,000 or 70,000 IU of vitamin D_3 per week for 12 weeks and were monitored for a total of 18 weeks.[25] The purpose of this study was to monitor the response of high dose supplementation (>35,000 IU/week) on vitamin D metabolites and potential withdrawal effects. More specifically, 24,25[OH]2D was monitored because a higher production of this vitamin D metabolite may decrease 25(OH)D concentrations. Both intervention groups had a significant increase in 25(OH)D and decrease in PTH by week six. However, by week 18 both the low and high dose supplemental groups had returned to baseline 25(OH)D measurements. The 24,25[OH]2D metabolite also increased throughout the intervention and remained significantly higher than baseline ($p<0.05$) at week 18. Interestingly, these findings indicate this metabolite may inhibit the activity of VDR; however, more research in this area is needed. Therefore, Owens and colleagues suggest a lower more frequent dose of vitamin D_3, with a gradual withdrawal, may be the most ideal intervention.[25] In contrast, Tomlinson and colleagues suggest daily D_3 supplementation and larger weekly doses have the same effectiveness regarding improving muscle strength.[23] Their meta-analysis of seven studies show consistent significant results of daily supplementation compared to conflicting results of weekly dose.

Vitamin D supplementation and physical performance has been assessed in a randomized placebo-controlled cohort study of athletes.[26] Baseline 25(OH)D was measured and suggested 70% of the subjects had insufficient 20(OH)D levels of <20 ng/mL. The intervention group received a daily dose of 5,000 IU vitamin D supplementation for eight weeks. This group demonstrated a significant improvement in the vertical jump and sprint performance protocols, while the placebo group exhibited no change. In a smaller randomized control trial of 30 male and female subjects, the effect of vitamin D supplementation on muscle power strength was observed. Of these 30 subjects, 37% exhibited 25(OH)D insufficiency at baseline (<30 ng/ml).[27] All subjects were randomly assigned to receive supplements of either 200 IU, 4,000 IU, or placebo for 28 consecutive days. Muscle power strength was assessed by a single leg plyo-press. Findings suggest 25(OH)D levels were positively correlated with muscle strength, but

supplementation among the 63% of subjects who were 25(OH)D sufficient (≥ 30 ng/ml) did not improve muscle strength.

In a later review by Tomblinson et al[23], vitamin D supplementation was also shown to increase muscle strength in those who were 25(OH)D deficient (≤ 32 ng/ml). Interestingly, a randomized dose-response study of 30 athletes supplemented with either placebo, 20,000 IU or 40,000 IU for 12 weeks found no correlation between 25(OH)D concentrations above 50 ng/ml and physical performance and muscle strength as measured by bench press, leg press and vertical jump height.[28] Cumulatively, these findings suggest a plateau of 25(OH)D in further improving muscle strength when serum 25(OH)D levels are sufficient.

Prolonged intense physical activity training can result in excessive bone turnover and incidence of stress fractures. The negative impact of vitamin D insufficiency on bone health through the calcium homeostasis mechanism presents additional high risk for bone fracture injury. In a randomized double-blind placebo controlled study, supplementation containing both vitamin D_3 (800 IU/day) and calcium (2000 mg/day) for 8 weeks was shown to decrease stress fracture incidence in 3,700 female Navy recruits aged 17-35 years of age.[29] Unfortunately, this study examined vitamin D_3 and calcium together, not separately.

A more recent study examined the effects of vitamin D supplementation on bone turnover in 68 adolescent females who presented with low 25(OH)D (<20 ng/mL) at baseline.[30] All subjects received weekly vitamin D_3 supplementation of 35,000 IU for four weeks. Although there was not a placebo group, there was an overall significant increase in 25(OH)D levels from baseline of 11.2 ± 6 ng/mL to 22.4 ± 9.2 ng/mL by the end of the study. In addition, PTH and bone turnover markers (BTMs) of osteocalcin and carboxy-terminal telopeptides of crosslinks of type 1 collagen (βCTX) significantly decreased in just four weeks. During bone resorption, βCTX is released into the bloodstream and can serve as a biomarker of bone degradation. Elevated βCTX may indicate increased bone resorption during times of growth or fracture healing. However, the role of vitamin D supplementation for fracture healing has produced conflicting evidence in the literature based on a review of 105 articles by Gorter and colleagues.[31] Articles published between the years 1984-2013 were gathered to explore the cellular effects and

clinical involvement of vitamin D in fracture healing. The researchers used four identifying characteristics when reviewing these articles including biomarkers of inflammation (IL-6), soft callus formation (IGF), hard callus formation (collagen 1), and remodeling (osteoclastogenesis). Each of these areas explored produced conflicting results. Thus, it is critical that vitamin D status in athletes (as well as other populations) are evaluated and supplementation is initiated as appropriate for a more proactive approach in preventing injury occurrence.

With any dietary supplementation, toxicity and adverse effects must be carefully considered and monitored. Vitamin D toxicity from sunlight or dietary intake has never been reported.[5] Vitamin D toxicity is more likely to occur from the overuse of supplementation or by faulty manufactured supplements. Symptoms of toxicity include hypercalcemia, frequent urination, excessive thirst, anorexia nausea, vomiting and possibly altered mental status. Research is mixed on kidney stone formation in relationship to high vitamin D levels.[6,32,33] This is most likely due to the many other possible contributing factors to stone formation such as age, dehydration, obesity, and certain medications (diuretics, antibiotics). However, many kidney stones are calcium based and could be impacted by high levels of vitamin D due to vitamin D's involvement in calcium homeostasis. It is crucial that individuals have their vitamin D checked prior to supplementation and routinely to provide treatment efficacy and to reduce the risk of adverse events.

A randomized clinical trial put forth by the Women's Health Initiative (WHI) found a positive correlation between urinary tract stone incidence with the use of calcium plus vitamin D supplements. ExaminationVitamin D only supplementation was not conducted.[32] A separate study that did analyze vitamin D status relative to kidney stone formation found 25(OH)D levels between 20-100 ng/mL were not associated with increased kidney stone incidence.[33] The same study reported positive correlations between BMI and age with kidney stone development, which is less likely a concern within an athletic population. Overall, toxicity levels and adverse effects of vitamin D are unlikely. No adverse effects have been reported with 70,000 IU weekly supplementation.[24] A no adverse effect limit (NOAEL) of 10,000 IU daily has been noted by the Institute of Medicine (IoM).[8]

Conclusion

Vitamin D has many important functions including calcium homeostasis, PTH regulation, bone and muscle health. The risk of vitamin D insufficiency in athletes is not only an expanding area of interest in research, but it is a growing topic in the sports medicine and sports nutrition fields with physical performance a top priority. Current evidence suggests increasing serum 25(OH)D levels may have beneficial effects on bone and muscle health in those who have depleted stores, while the evidence remains unclear of the same benefits for increasing already sufficient 25(OH) levels.[17,24-27] Higher serum levels of vitamin D seem to overall be inversely associated with reduced injury rates and improved sports performance. Sun UV exposure is the primary source of Vitamin D and can be difficult to accurately account for, thus will often confound findings when assessing response to vitamin D supplementation. It is crucial that this UV exposure be considered in clinical settings. There remains controversy on the topic of vitamin D and there is a need for clarity and standardization of levels defining vitamin D deficiency and insufficiency as well as a protocol for appropriate supplement dosage. Without this standardization, replicable research is a significant challenge. At the same time, standardization is a difficult development without the replicable research. Once gold standard methods are developed, supplement protocol and serum values can be directly comparable between studies and clinical settings. In addition to standardization, future research should control for co-founding variables such as UV exposure, supplement compliance, sport type (weight bearing versus non weight bearing), playing time, and baseline 25(OH)D concentrations.

Table 3. Excluded Articles

Excluded Articles	Reason for Exclusion
Safadi FF, et al., Osteopathy and resistance to vitamin D toxicity in mice null for vitamin D binding protein, 1999.	Date, non-human subject
Gorter EA, et al., The role of vitamin D in human fracture healing: A systematic review of the literature, 2014.	In Vitro
Meier C,et al., Supplementation with Oral Vitamin D3 and Calcium During Winter Prevents Seasonal Bone Loss: A Randomized Controlled Open-Label Prospective Trial, 2004	Published before 2008

Table 4. Summary of Bone Health Studies

Study Author/Year/Design	Study Population	Methods and Intervention	Measured Markers	Significant Outcomes
Maroon et al., 2015, cohort	80 NFL male athletes aged 26.5±3.7 yr	25(OH)D measured to compare race and BF reports over 2 yr	25(OH)D (≥32=sufficient, ≤20=deficient), BMD, BF hx	25(OH)D of blacks significantly lower than whites. 25(OH)D significantly lower in players with hx of 1+ BF
Miller, et al., 2016, retrospective Cohort	124 male (n=42) and female (n=82) subjects aged 43.9±17.5 yr	Examine 25(OH)D levels in pts with SF	25(OH)D, SF	83% of pts had 25(OH)D levels <40 ng/mL
Burgi, et al., 2011, case-control cohort	1,200 female Navy recruits aged 19.5 ± 1.7 yr	Determine 25(OH)D level with greatest risk of SF	25(OH)D, tibia and fibula SF	Half the risk of SF in those with 25(OH)D >40ng/mL compared to those with <20 ng/mL
Grieshober, et al., 2018, epidemiology study	279 NBA combine male athletes with	Data obtained and analysed to determine associations	25(OH)D (≥30= sufficient, 20-29= insufficient, ≤20= deficient), bone SF	25(OH)D deficiency in 32.3%, insufficiency in 41.2%, and sufficient levels in 26.5% of subjects.

	a mean age of 21.5 yr	between vit D status, SF risk and NBA draft status	hx, NBA draft status	25(OH)D not predictive of SF risk. Pts with deficient 25(OH)D had a significantly lower rate of NBA draft. NBA draft rate increased with increasing 25(OH)D levels
Lewis et al., 2013, randomized placebo controlled	32 male and female (41%) swimmers aged 19-21 yr with 25(OH)D ≥32ng/mL	6 mo. vit D supplement (4,000 IU (n=19) or PLA (n=13)	25(OH)D (≥32=sufficient, ≤20=deficient), BMD, IL6	16% dropped below 32ng/mL (n=1 VIT D, n=4 PLA). Mean changes in 25(OH)D were +1ng/mL (VIT D) and -20ng/mL (PLA). No significant findings of BMD or IL6
Lappe et al., 2008, randomized double-blind, placebo controlled	3700 female navy recruits median aged 19 yr	Daily vit D (800 IU) and calcium (2000mg) supplement (n=1852) or PLA (n=1848) for 8 wk	SF incidence	Treatment group had 21% lower incidence of SF compared to PLA.
Sulimani et al., 2017, cohort interventional study	68 females vit D deficient aged 15.1 ± 1.7 yr	Weekly 35000 IU vit D supplement for 4 wk	25(OH)D (≤20=deficient), PTH, βCTX, osteocalcin	Significant increase in 25(OH)D, significant decrease in PTH, osteocalcin and βCTX

List of Abbreviations: yr= years; 25(OH)D= 25-hydroxyvitamin D; BF= bone fracture; hx= history; pts= patients; SF= stress fracture; vit D= vitamin D; PLA= placebo; mo.= months; BMD= bone mineral density; IL6= interleukin 6; wk= weeks

Table 5. Summary of Muscular Health Studies

Study Author/Year/Design	Study Population	Methods and Intervention	Measured Markers	Significant Outcomes

Rebolledo et al., 2018, retrospective Cohort	214 NFL male athletes aged 26.6±4.5 yr	25(OH)D, Race, and MI collected to compare associations	25(OH)D (≥32= sufficient, 20-31= insufficient, ≤20= deficient), MI hx, race	Insufficient 25(OH)D found in 49% of pts and 10% with deficiency. Black race and MI was associated with lower 25(OH)D levels
Grimaldi et al., 2014, cross sectional	419 male (48%) and female (52%) ages 20-76 yr	Investigate the relation of vit D status and arm and leg Isometric and isokinetic strength using computerized dynamometry	25(OH)D, hand grip, elbow and knee flexion/extension	25(OH)D significantly positively correlated with isometric and isokinetic arm strength and isometric leg MS when controlling age and gender
Tomlinson, et al. 2015, systematic review with meta-analysis	310 male and female (67%) aged 18-40 yr, mean ages from 21.5 to 31.5 yr	Included 7 RCT lasting 4 wk-6 mo.	25(OH)D, vit D supplement (4000 IU/d-60000 IU/wk, upper and lower limb MS	All doses of vit D significantly increased MS of both upper and lower limbs.
Close et al., 2013, double-blind placebo-controlled	10 male soccer athletes aged 18 yr	5000 IU daily vit D supplement (n=5) or PLA (n=5) for 8 wk	25(OH)D (≥40=sufficient,≤20=deficient), bench press, squat, sprint, vertical jump	Sprint times, vertical jump, 25(OH)D significantly increased in the vit D group.
Barker, et al., 2012, randomized double-blind placebo-controlled	30 male and female (n=15) aged 18-45 yr	Daily 4000 IU vit D (HD), 200 IU vit D (LD), or PLA for 28 days	25(OH)D (≥30=sufficient, ≤20=deficient), IL6, MS (leg)	63% of pts vit D sufficient at BL. 25(OH)D and IL6 decreased in PLA. LD maintained 25(OH)D, increased IL6. HD increased 25(OH)D, maintained IL6. 25(OH)D associated with MS, not supplementation

Close et al., 2013, block randomized dose-response	30 male athletes aged 20-24 yr	Weekly 20000 IU (LD), 40000 IU (HD), or PLA for 12 wk. All groups included 10 subjects.	25(OH)D(≤20= deficient), bench press, leg press, vertical jump	57% of pts 25(OH)D deficient at BL. 25(OH)D increased in LD and HD groups to achieve >20ng/mL, decreased in PLA. No effect on physical performance markers

List of Abbreviations: yr= years; 25(OH)D= 25-hydroxyvitamin D; MI= muscle injury; hx= history; pts= patients; vit D= vitamin D; MS= muscle strength; wk= weeks; RCT= randomized control trial; mo.= months; PLA= placebo; IL6= interleukin 6; BL= baseline; HD= high dose; LD= low dose

Table 6. Summary of Vitamin D Supplementation Studies

Study Author/Year/Design	Study Population	Methods and Intervention	Measured Markers	Significant Outcomes
Lewis et al., 2013, randomized placebo controlled	32 male and female (41%) swimmers aged 19-21 yr with 25(OH)D ≥32ng/mL	6 month daily vit D supplement (4,000 IU (n=19) or PLA (n=13)	25(OH)D (≥32=sufficient, ≤20=deficient), BMD, IL6	16% dropped below 32ng/mL (n=1 Vit D, n=4 PLA). Mean changes in 25(OH)D were +1ng/mL (Vit D) and -20ng/mL (PLA).
Tomlinson, et al. 2015, systematic review with meta-analysis	310 male and female (67%) aged 18-40 yr	Seven RCT lasting 4 wk-6 mo. Vit D supplement of 4000 IU/d-60000 IU/wk	25(OH)D, MS: grip, bench press, chest press, leg press, squats	All doses of vit D significantly increased MS of both upper and lower limbs.
Owens, et al., 2017, block randomized	42 male elite athletes 26 ± 3 yr	Block randomized on BL 25(OH)D into either 70000 IU (HD) or 35000 IU (LD) weekly vit D supplement for 12 wk, monitored for 18 wk	25(OH)D, PTH, $24,25[OH]_2D$, $1,25[OH]_2D_3$	All doses had significant increases in 25(OH)D and $1,25[OH]_2D_3$. HD significantly increased 24,25[OH]2D. PTH decreased in both groups. LD recommended.

Close et al., 2013, double-blind placebo-controlled	10 male soccer athletes aged 18 yr	5000 IU daily vit D supplement (n=5) or PLA (n=5) for 8 wk	25(OH)D (≥40=sufficient,≤ 20=deficient), bench press, squat, sprint, vertical jump	Sprint times, vertical jump, 25(OH)D significantly increased in the vit D group.
Barker, et al., 2012, randomized double-blind placebo-controlled	30 male and female (n=15) aged 18-45 yr	Daily 4000 IU vit D (HD), 200 IU vit D (LD), or PLA for 28 days	25(OH)D (≥30=sufficient, ≤20=deficient), IL6, MS (leg)	63% of pts vit D sufficient at BL. 25(OH)D and IL6 decreased in PLA. LD maintained 25(OH)D, increased IL6. HD increased 25(OH)D, maintained IL6. 25(OH)D associated with MS, not supplementation
Close et al., 2013, block randomized dose-response	30 male athletes aged 20-24 yr	Weekly 20000 IU (LD), 40000 IU (HD), or PLA for 12 wk. All groups included 10 subjects.	25(OH)D(≤20 ng/mL= deficient), bench press, leg press, vertical jump	57% of pts 25(OH)D deficient at BL. 25(OH)D increased in LD and HD groups to achieve >20ng/mL, decreased in PLA. No effect on physical performance markers
Lappe et al., 2008, randomized double-blind, placebo controlled	3700 female navy recruits median aged 19 yr	Daily vit D (800 IU) and calcium (2000mg) supplement(n=1852) or PLA (n=1848) for 8 wk	SF incidence	Treatment group had 21% lower incidence of SF compared to PLA.
Sulimani et al., 2017, cohort interventional study	68 females vit D deficient (<20 ng/mL) aged 15.1 ± 1.7 yr.	Weekly 35000 IU vit D supplement for 4 wks	25(OH)D (≤20=deficient), PTH, βCTX, osteocalcin	Significant increase in 25(OH)D, significant decrease in PTH, osteocalcin and βCTX

List of Abbreviations: yr= years; 25(OH)D= 25-hydroxyvitamin D; vit D= vitamin D; PLA= placebo; BMD= bone mineral density; IL6= interleukin 6; RCT= randomized control trial; wk= weeks; mo.= months; MS= muscle strength;

BL= baseline; HD= high dose; LD= low dose; PTH= parathyroid hormone; $24,25[OH]_2D$,= 24,25-dihydroxyvitamin D; $1,25[OH]_2D_3$ =1,25-dihydroxyvitamin D; SF= stress fracture; βCTX= C-terminal telopeptide

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