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Clinical Relevance of Optimizing Vitamin D Status in Soldiers to Enhance Physical and Cognitive Performance

Laurel M. Wentz, PhD; Jerad D. Eldred, 18D;
Michael D. Henry, MD; Cristóbal S. Berry-Cabán, PhD

ABSTRACT

Vitamin D deficiency initiates a loss of combat effectiveness by impairing physical and cognitive functioning of combat Operators. Synthesized in response to sunlight and consumed in the diet, vitamin D functions as a hormone and regulates gene expression for nearly 300 genes throughout the human body. These target genes are involved processes essential to combat operations, such as immune function, response to stress, inflammation, and regulation of calcium movement. Since widespread vitamin D deficiency is observed across the U.S. population, poor vitamin D status is expected in Servicemembers. Physical conditions linked to vitamin D deficiency include increased risk for muscle or bone injury, muscle weakness, and reduced neuromuscular function. Hormonally, vitamin D levels have been positively correlated with testosterone levels. Vitamin D deficiency is also associated with cognitive decline, depression, and may prolong recovery following mild traumatic brain injury (mTBI). Since vitamin D deficiency elevates systemic inflammation, poor vitamin D status at the time of brain injury may prolong the inflammatory response and exacerbate postconcussive symptoms. Furthermore, veterans with mTBI experience chronic endocrine dysfunction. While vitamin D status has not been assessed post-mTBI, it is plausible that vitamin D levels are altered along with testosterone and growth hormone, raising the question of whether vitamin D deficiency results from trauma-related hormonal abnormalities or whether vitamin D deficiency increases the risk for endocrine dysfunction. Through its association with testosterone production, vitamin D deficiency may increase the risk for posttraumatic stress disorder (PTSD) since testosterone levels are altered in veterans with PTSD. Therefore, vitamin D status has a significant impact on Operator health and performance. Supplementing vitamin D to deficient Operators provides a noninvasive and low-cost intervention to maintain combat force.

KEYWORDS: *vitamin D, 25-hydroxyvitamin D, inflammation, neuroprotection, musculoskeletal performance, combat readiness*

Introduction

Vitamin D deficiency threatens the physical and cognitive functioning of combat Operators. While dietary intake contributes to vitamin D status, it is also synthesized in the skin when exposed to specific UV wavelengths, thereby distinguishing it from other vitamins. Vitamin D functions as a hormone and regulates gene expression for pathways essential to physical and cognitive performance. Hormonal imbalances, including vitamin D deficiency, may result from a combination of environmental exposures, poor nutrition, and strenuous training. Failing to correct vitamin D status in a deficient Soldier has the potential to limit Operator function, reducing combat power and effectiveness. Conditions linked to vitamin D deficiency include loss of muscle strength, reduced testosterone synthesis, and increased risk of muscle/bone injury, cognitive decline, depression, and postconcussive symptoms.

The recent explosion of vitamin D research has invited a mixture of criticism and acclaim as vitamin D is now recognized to have more biological functions than were previously understood. Thus, conflicting recommendations for optimal status and dietary intake of vitamin D have created confusion among members of the medical community.

The purpose of this review is to highlight the role of vitamin D in physical and cognitive functions essential to combat operations along with consequences of untreated deficiencies. The clinical relevance of assessing vitamin D status is described as it relates to physiological operations required for optimal health and performance.

Special Operation Forces Relevance

Vitamin D deficiency is widespread across the Special Operation Forces (SOF) population. Preliminary data from a review of medical records show that 314 unique vitamin D assessments were ordered for SOF personnel at Womack Army Medical Center (WAMC) over the previous 2 years.¹ More than half of the Servicemembers

tested had deficient or insufficient levels of serum vitamin D (Table 1). This contrasts with a study that measured serum vitamin D levels in 1993 during a Special Forces Assessment and Selection (SFAS) Course that found vitamin D levels within the normal range, suggesting that SOF vitamin D levels have decreased over the past two decades.² Since SFAS occurs in the same region as WAMC, geography or climatology does not explain the differences in vitamin D status. These vitamin D levels persist despite the use of dietary supplements. According to published survey results, 46% of Special Forces Operators consume multivitamins (although the vitamin D content in most multivitamins is inadequate to maintain sufficient status).³

Table 1 Vitamin D Status in SOF Personnel.

	Sample	Mean ± SD (ng/mL)	Range (ng/mL)
Wentz et al., 2013	SOF personnel (n = 314)	30 ± 10	10–63
Fairbrother et al., 1995	SFAS Soldiers (n = 100)	61 ± 16	34–100

Note: The Army Medical Department (AMEDD) normal range 30–100ng/mL.

History of Vitamin D

Deficiency of vitamin D (commonly referred to as “rickets” when it occurs in children) was first described in the mid-1600s by Whistler and Glisson,⁴ but for decades thereafter, no progress was made in identifying the cause. In 1918, Mellanby described the deficiency of a fat-soluble nutrient as the cause for rickets.⁵ Shortly thereafter, Goldblatt and Soames demonstrated that skin exposed to sunlight produced a substance with similar properties to this fat-soluble nutrient.⁶ This led to the discovery of the chemical structure of vitamin D by Windaus.⁷

Once the role of vitamin D in maintaining calcium homeostasis and bone health was understood, interest in vitamin D waned as rickets became a preventable condition. However, regulation of bone turnover turned out to be only one of its numerous functions, showing that substantial work remains to diagram vitamin D physiology. Twenty-first century technology has identified vitamin D receptors and metabolizing enzymes throughout the body, including the brain, muscle, prostate, testes, breast, and macrophages.⁸ This widespread distribution of receptors and enzymes supports the relationship between vitamin D status and alterations in gene expression across a variety of conditions.⁹

Vitamin D Metabolism

Vitamin D is required for a range of biological activities essential to optimal physical and cognitive health. Synthesized in the skin and found in few dietary sources,

vitamin D undergoes a series of biochemical changes to convert to its active form. Endogenous synthesis occurs in response to UVB photons from sunlight to form vitamin D₃ from cholesterol. Dietary sources include vitamin D₃ as well as the plant form of vitamin D₂. Neither vitamin D form has biological activity until a series of enzymes alter its structure. First, vitamin D is hydroxylated in the liver to produce 25-hydroxyvitamin D [25(OH)D]. Then, 25(OH)D is further hydroxylated in the kidney to produce 1,25-dihydroxyvitamin D [1,25(OH)₂D], which is the active form. In addition to the liver and kidney, vitamin D hydroxylating enzymes have been identified in other tissues. Vitamin D increases or decreases gene expression of specific genes by 1,25(OH)₂D binding to vitamin D receptors (VDRs) on target cells (Figure 1). As a result, vitamin D plays a role in regulating expression for nearly 300 genes throughout the human body.⁹ Relevant to SOF Operators, these target genes are involved in immune function, response to stress, inflammation, and regulation of calcium movement.

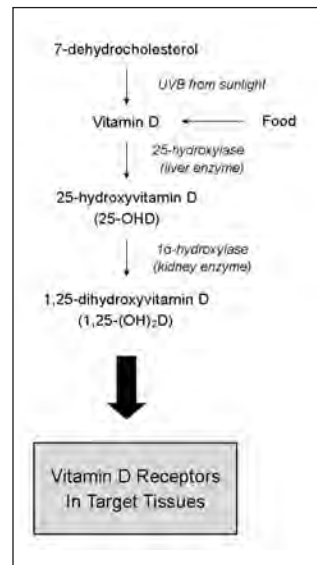
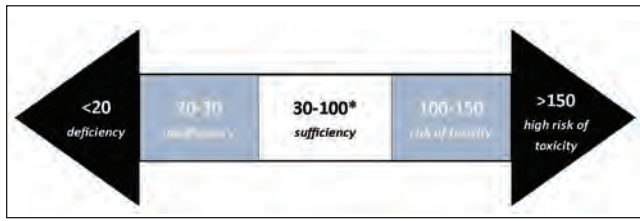


Figure 1 Vitamin D metabolism.

Vitamin D Deficiency in Servicemembers

Since activation of vitamin D is tightly regulated and 1,25(OH)₂D is degraded quickly, measurement of this form is of little clinical significance. Therefore, the circulating form 25(OH)D is used for assessment of status. The 2011 Institute of Medicine report suggests vitamin D deficiency be defined as serum 25(OH)D less than 20ng/mL, based on evidence related to bone health.¹⁰ However, significant amounts of research support sufficient vitamin D as 25(OH)D levels between 30 and 100ng/mL.¹¹ This range is recommended by the International Endocrine Society to optimize physical and cognitive functioning (Figure 2).¹¹ The standards of care in the Army Medical Department (AMEDD) follow the ranges recommended by the Endocrine Society, although routine vitamin D screening has not been implemented.¹²

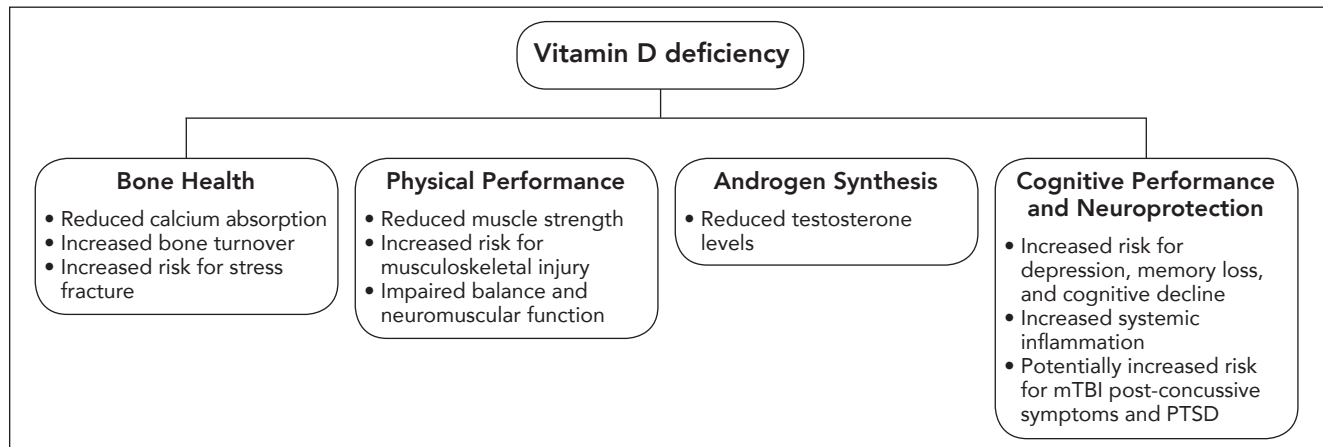
Figure 2 Ranges for serum 25-hydroxyvitamin D levels in ng/mL. *40–50 ng/mL has been recommended as optimal vitamin D status. Adapted from Endocrine Society Clinical Practice Guideline.⁵



No data have been published on the prevalence of vitamin D deficiency in active duty personnel. However, analysis of archived serum samples from 990 Servicemembers found that 35% of subjects had serum 25(OH)D levels less than 20ng/mL.¹³ Fifty-seven percent of female recruits entering basic training had serum 25(OH)D levels less than 30ng/mL, increasing to 75% of recruits with low vitamin D after 8 weeks despite outdoor training.¹⁴ Mean serum 25(OH)D levels in 1200 U.S. Navy female recruits were 30ng/mL,¹⁵ while 204 male Finnish recruits had mean 25(OH)D levels of 18ng/mL.¹⁶ Male Lithuanian soldiers had mean 25(OH) levels of 12ng/mL, with 95% of the 262 men deficient in vitamin D.¹⁷

These vitamin D levels are similar to those measured in NHANES data, which estimate that 32% of the U.S. population is deficient in vitamin D.¹⁸ In fact, many experts argue that optimal vitamin D status is serum 25(OH)D between 40 and 50ng/mL, based on the inability to store vitamin D in muscle and fat tissue at lower levels.¹⁹ Serum samples from lifeguards and Tanzania residents show that individuals with outdoor lifestyles have 25(OH)D ranging 45 to 65ng/mL, indicating these levels reflect evolutionary human sun exposure.²⁰ Based on these reports, it is expected that a significant proportion of combat Operators have insufficient levels of vitamin D, limiting their physical and cognitive functioning and potentially compromising their overall performance.

Figure 3 Summary of symptoms related to vitamin D deficiency.



Serum vitamin D levels in the United States have decreased over the past few decades.¹⁸ Sunlight generally contributes about 90% of vitamin D, with the remaining 10% coming from dietary sources.²⁰ Risk factors for vitamin D deficiency include minimal sunlight exposure, darker skin pigmentation, use of sun block, and wearing protective clothing.

Outdoor training in tactical gear prevents adequate skin exposure, as evidenced in female U.S. Army recruits whose vitamin D levels decreased throughout basic combat training, despite outdoor activities during autumn in South Carolina.¹⁴ The pattern of vitamin D seasonality in the United States shows a peak in August and a nadir in February.²¹ For most U.S. latitudes north of Atlanta, GA (33.7°N), UV radiation is inadequate for sufficient endogenous synthesis of vitamin D during the winter months.¹¹ Therefore, individuals training in these regions are dependent on dietary sources of vitamin D.

Good natural sources of vitamin D₃ are limited to fatty fish (salmon, mackerel, tuna) and egg yolks. Additionally, the United States mandates that all dairy milk be fortified with 100IU vitamin D per 8 ounces. Manufacturers may choose to fortify additional dairy products, nondairy substitutes, or grains. Vitamin D₂ is another dietary form found in irradiated mushrooms, as well as some fortified foods and supplements. However, the limited sources of dietary vitamin D may be insufficient to meet vitamin D requirements, especially when sunlight exposure is limited.

Vitamin D Deficiency Inhibits Physical and Cognitive Performance

Vitamin D receptors and enzymes are present throughout tissues of the body and contribute to a variety of functions related to bone health, physical performance, androgen synthesis, cognitive performance, and neuroprotection (Figure 3). Vitamin D deficiency leads to

hormonal abnormalities, increased inflammation, and reduced muscle strength, all of which will inhibit optimal Operator functioning.

Bone Health

Essential to the regulation of calcium homeostasis and bone metabolism, vitamin D facilitates absorption of dietary calcium following activation by parathyroid hormone (PTH). Poor calcium absorption from the gastrointestinal tract elevates PTH levels, forcing bone to free enough calcium to raise extracellular levels and promoting bone loss via excessive bone degradation. Elevated rates of bone remodeling weaken bones and increase fragility, raising the risk for stress fractures during military training.²² In a prospective study of men in the Finnish Defense Forces, baseline measurements of serum 25(OH)D were significantly lower in recruits who developed stress fractures during basic training.²³ Similarly, female U.S. Navy recruits with serum 25(OH)D levels lower than 39.9ng/mL had a higher risk of stress fractures during the first 6 months of active duty compared with recruits with higher 25(OH)D levels.¹⁵ Elite male combat recruits from the Israeli Defense Forces who developed stress fractures had significant deficits in dietary vitamin D intake compared with their peers without stress fractures.²⁴

While PTH levels did not differ between stress fracture groups in these Operators, other researchers have shown that elevated PTH increases the risk for stress fractures in Servicemembers.²⁵ Prolonged physical activity increases PTH in response to depressed serum calcium levels.²⁶ As a result, combat Operators engaged in strenuous training may have increased requirements for vitamin D compared with the normal population. Failure to meet these needs will lead to hormonal alterations and changes in bone turnover. In Lithuanian servicemembers, serum 25(OH)D showed a weak negative correlation with PTH levels that is likely to increase rates of bone degradation.¹⁷ Sex hormone binding globulin, a measure of estrogen and testosterone, was positively associated with both 25(OH)D and markers of bone turnover in male Finnish recruits, suggesting that vitamin D is essential to hormonal regulation of bone homeostasis.¹⁶

Physical Performance

Recent evidence has established a role of vitamin D in physical performance, showing an association of poor vitamin D status with reduced muscle strength and increased injury risk.²⁷ For example, football players with muscle injuries had a mean serum 25(OH)D level of 19.9ng/mL that was significantly lower than the mean level of 24.7ng/mL measured in uninjured team members.²⁸ In another group of athletes, vitamin D supplementation during the winter months was associated with fewer injuries compared with nonsupplemented athletes.²⁹

Intense exercise produces inflammatory cytokines that contributes to postexercise muscle damage. Vitamin D modulates the postexercise inflammatory response, reducing muscle weakness and enhancing muscle recovery between exercise sessions.³⁰ In endurance runners, serum 25(OH)D levels were inversely correlated to inflammatory cytokines, suggesting that maintaining optimal vitamin D status suppresses the inflammatory response associated with physical training.³¹ Further research shows that inflammatory cytokines are elevated in active adults with poor vitamin D status, reinforcing a negative correlation between vitamin D levels and inflammatory cytokines.³² Thus, optimal vitamin D levels appear to regulate the postexercise inflammatory response, reducing the risk for muscle damage and potential injury.

Increased risk for musculoskeletal injury observed in vitamin D-deficient athletes may develop from muscle weakness or myopathy since chronic vitamin D deficiency has been associated with muscle weakness, musculoskeletal pain, and poor balance.³³ Vitamin D-supplemented athletes sustained fewer injuries and improved their muscle strength and power, while non-supplemented peers had no change or slight regression in these measurements.²⁹ In healthy adults, higher serum 25(OH)D levels were correlated with upper and lower extremity muscle strength.³⁴ Professional soccer players with vitamin D deficiency had lower leg muscle mass compared with players with higher vitamin D levels.³⁵ Vitamin D deficiency has also been linked to atrophy of type II muscle fibers, which are responsible for bursts of speed and power.³⁶ Therefore, correcting deficiency can increase type II muscle fiber diameter and translate to improved physical performance, as evidenced in professional athletes. Eight weeks of vitamin D supplementation significantly improved vertical jump and 10-m sprint speed in deficient professional European soccer players.³⁷ Peak lower extremity function has been observed with 25(OH)D levels greater than 40ng/mL, likely because type II muscle fibers are involved in balance and neuromuscular function.³⁸ Along these lines, vitamin D supplementation in deficient older adults improved balance, reaction time, and functional coordination.³⁹

Androgen Synthesis

One potential mechanism for improved physical performance with higher vitamin D status is its interaction with androgenic activity.³⁴ Vitamin D may play a role in regulating testosterone production, as evidenced by the identification of vitamin D receptors and metabolizing enzymes in the testes.⁴⁰ If testosterone production decreases due to vitamin D deficiency, then physical performance could be impaired. The combination of strenuous training and poor nutrition lower testosterone levels and have been shown to result in loss of muscle strength

and power.⁴¹ In a large sample of men, serum 25(OH)D levels were associated with total testosterone even after adjusting for age and body mass index.⁴² A follow-up study supplemented a subset of those men with 3332IU vitamin D per day for 1 year.⁴³ At baseline, both groups of men had mean 25(OH)D levels in the deficient range. However, after 1 year of vitamin D supplementation, 25(OH)D levels were significantly raised as well as all measures of testosterone. No significant changes occurred within the placebo group, supporting the theory that vitamin D deficiency inhibits androgen synthesis. Emerging evidence strengthens support for the relationship between vitamin D and testosterone production by showing that 25(OH)D production occurs in Leydig cells of testes, which are the site of testosterone production.⁴⁴ Therefore, Operators with preexisting vitamin D deficiency may be at increased risk for deficits in testosterone level.

Cognitive Performance and Neuroprotection

Vitamin D receptors and metabolizing enzymes have been identified in the human brain, establishing support for a role of vitamin D in brain function and development.⁴⁵ Further research have linked vitamin D deficiency to increased risk for certain psychiatric and neurological diseases such as depression, schizophrenia, autism, multiple sclerosis, Alzheimer's disease, and dementia.^{45,46} As a regulator of gene transcription, vitamin D targets neural genes that affect a variety of behavioral and biochemical processes. Animal models have shown that vitamin D deficiency slows learning and increases anxiety,⁴⁷ while human studies have correlated low vitamin D levels with depression⁴⁸ and accelerated cognitive decline.⁴⁹ Elevated levels of inflammatory cytokines have been correlated with both depression and vitamin D deficiency, suggesting that vitamin D suppresses excess neural inflammation and maintains cognitive health.⁴⁷

Due to its role in cognitive function and regulation of the inflammatory response, optimal vitamin D status may provide neuroprotection in mild traumatic brain injury (mTBI). Since chronic vitamin D deficiency has been linked to a heightened acute inflammatory response, vitamin D deficiency at the time of brain injury could exacerbate secondary damage due to excess inflammation, worsening postconcussive symptoms and keeping an Operator from returning to duty. In response to biomechanical forces, mTBI stimulates a cascade of metabolic events including axonal injury, damaged cellular membranes, disrupted ion exchange, as well as reduced cerebral blood flow, inflammation, and cellular death.⁵⁰ While the acute release of inflammatory cytokines appears to be neuroprotective by promoting tissue repair, prolonged inflammation contributes to oxidative stress along with neurotoxicity and cellular death. As a key regulator of inflammatory cytokine, vitamin D may

provide resilience to mTBI by limiting the inflammatory response following impact. In an animal TBI model, vitamin D deficient rats had elevated levels of inflammatory markers at baseline and postinjury compared with vitamin D sufficient animals.⁵¹ Postinjury treatment with vitamin D was inferior to maintaining sufficient levels preinjury. Prolonged inflammation is linked to poor injury outcomes, which has been supported by higher levels of inflammatory cytokines measured within 24 hours of injury correlating with more severe brain injury in humans.⁵² Vitamin D deficiency restricts regulation of cytokine production, thereby allowing sustained inflammatory response to injury.⁵³ This prolonged inflammatory response to mTBI increases injury severity and presents an appropriate target for future research aimed at minimizing concussive symptoms. As of 2013, no human studies have looked at vitamin D status before or after mTBI.

Vitamin D deficiency likely prolongs mTBI recovery owing to its role in cognitive function and neuroprotection. While vitamin D status has been not be examined in human mTBI patients, research has established that endocrine dysfunction results from mTBI. Altered hormones were found in 42% of male veterans who had at least one mTBI related to blast exposure, compared with no evidence of dysfunction in veterans who had deployed but never sustained mTBI.⁵⁴ Hormone deficiencies were observed most frequently in testosterone and insulin growth factor I (indicator of growth hormone status). Evidence of endocrine dysfunction following mTBI suggests that vitamin D levels may also be altered postinjury, raising the question of whether vitamin D deficiency results from trauma-related hormonal abnormalities or whether vitamin D deficiency increases the risk for endocrine dysfunction. Cognitive symptoms linked to vitamin D deficiency are similar to those observed in endocrine dysfunction and post-concussive syndrome, such as memory loss, depression and increased risk for posttraumatic stress disorder (PTSD).^{47,54,55} Although vitamin D status has not been assessed in brain injury, the combination of vitamin D and progesterone has been shown to be an effective treatment for TBI. A human trial treated severe TBI patients with 200IU/kg (>10,000IU total) vitamin D per day during the first 5 days after injury in combination with progesterone.⁵⁶ The vitamin D-plus-progesterone treatment group experienced greater recovery compared with progesterone alone or placebo, supporting a role of vitamin D in accelerating brain repair.

Thus, research that monitors vitamin D levels in Operators with mTBI is needed, especially considering that vitamin D status may influence symptoms of PTSD and has been linked to risk of suicide. Through its association with testosterone production, vitamin D deficiency may contribute to symptoms of PTSD, such as depression,

anxiety, and sleep impairment. Vitamin D levels have not been assessed in PTSD patients, but testosterone levels are altered in veterans with PTSD.^{57,58} As discussed, testosterone levels have been positively correlated with vitamin D levels,⁴² and vitamin D supplementation increased testosterone levels in vitamin D-deficient men.⁴³ This suggests that hypogonadism is influenced by vitamin D status. Furthermore, low vitamin D levels have been linked to increased risk of suicide in active duty Servicemembers, reinforcing that vitamin D has an important role in mental health.¹³

Recommendations

The IOM set the vitamin D Recommended Dietary Allowance at 600IU/day and a tolerable upper intake level of 4000IU/day.¹⁰ However, many experts suggest that most adults require 1500–2000/per day to maintain blood levels above 30ng/mL.¹¹ Treatment of vitamin D deficiency generally requires supplementation of 50,000IU/week for 8 weeks or until serum 25(OH)D exceeds 30ng/mL, followed by a maintenance dose of 1500–2000IU/day. While dietary supplements are available as vitamin D₃ or D₂, research suggests that vitamin D₃ is more effective at increasing serum 25(OH)D due to its more efficient hydroxylation and greater affinity for VDR.⁵⁹

Vitamin D is toxic at high doses, manifesting initially as elevated calcium and phosphate and then as calcification of soft tissue. However, vitamin D intoxication is rare. Healthy men have supplemented with 10,000IU vitamin D₃/day for 5 months without adverse effects.⁸ Further evidence shows that subjects supplemented with 50,000IU vitamin D/week for 8 weeks followed by 50,000IU vitamin D every other week for 6 years experienced no toxicity, changes in calcium status, or kidney stones.⁶⁰ Vitamin D endogenous synthesis is regulated tightly. Therefore, if Operators are exposed to UV radiation with high vitamin D levels, endogenous vitamin D synthesis will be limited, thereby avoiding toxicity. An important distinction in clinical recommendation is to treat vitamin D deficiency rather than indiscriminate pharmacological supplementation. Most research indicates that no further benefits ensue with serum 25(OH)D levels exceeding 40 to 50ng/mL.

Limitations and Future Directions

Preliminary data show that vitamin D deficiency is widespread across SOF personnel. However, these data are retrospective and do not provide accurate prevalence of vitamin D deficiency in Servicemembers. Nevertheless, further analysis may identify significant relationships between vitamin D status and other laboratory measurements to design future studies aimed

at optimizing human performance in SOF. Prospective unitwide screening of vitamin D status and randomized placebo-controlled supplementation trials will elucidate the benefits of optimizing vitamin D status in deficient Servicemembers. Most notably, vitamin D status may affect recovery from mTBI due to its role in regulating inflammatory cytokines. To date, human studies have not evaluated vitamin D status in mTBI, although vitamin D has shown potential as treatment following TBI.⁴⁹

Conclusion

Implementing an aggressive clinical intervention to reduce vitamin D deficiency is paramount in addressing related cognitive and physical performance deficits. Vitamin D supplementation presents a safe, non-invasive, manageable, and low-cost intervention for maintaining health within the force. Evidence suggests that optimal vitamin D levels may provide resilience to mTBI by modifying the inflammatory response. Many of the chronic symptoms associated with mTBI such as depression, balance problems, and cognitive decline are also associated with vitamin D deficiency. Furthermore, these symptoms are associated with endocrine dysfunction and deficiencies in testosterone and growth hormone, which may be regulated by vitamin D.

There is additional evidence to support that vitamin D deficiency may have a role in PTSD related to its association with testosterone production and relationship with other mental health disorders. Furthermore, vitamin D deficiency has the potential to limit physical performance via reduced muscle strength and poor balance. Unidentified vitamin D deficiencies are likely contributing to loss of combat power and effectiveness. With deficiency potentially widespread, vitamin D status has implications in physical training as well as cognitive functioning related to the treatment and prevention of mTBI and PTSD. While vitamin D is one component of multifactorial conditions, correcting vitamin D deficiency will eliminate a treatable etiology that inhibits progression of treatment for cognitive and/or performance impairments.

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Disclosures

The authors have indicated they have no financial relationships relevant to this article to disclose. No funding was used to support this work.

Dr. Wentz is an assistant professor in the Department of Nutrition Science at East Carolina University. Prior to joining the ECU faculty, Dr. Wentz was the Performance Dietitian for 3rd Special Forces Group (Airborne) in Fort Bragg, NC. During her time working with this Group, she collaborated with physicians to treat vitamin D deficiencies in Servicemembers in addition to conducting nutrition assessments and implementing dietary treatment plans for combat Operators. Dr. Wentz is currently conducting research aimed at identifying clinically relevant correlations between vitamin D and associated hormones to identify potential treatment strategies as well as investigating the potential relationship of vitamin D levels with post-concussive symptoms following TBI. E-mail: wentzl@ecu.edu.

MSG Eldred is the senior enlisted medical advisor for 3rd Special Forces Group (Airborne), Fort Bragg, NC. He advises the Group Command Team, Group/ BN Surgeons, 184 Special Forces Medical Sergeants, and Group Staff on all aspects of medical operations. MSG Eldred tracks and coordinates the care for the Group's sick and wounded warriors to include attachments during deployment while also planning, resourcing, and overseeing all medical training within the Group. MSG Eldred graduated from the Special Forces Qualification Course in April 2005 before holding the position of Special Forces Medical Sergeant Operational Detachment Alpha (ODA) 336, 1st Battalion, 3rd Special Forces Group (Airborne). Additional

duty positions included Special Forces Medical Sergeant for a “Special Projects Team” as well as Battalion Medical Sergeant for 1st Battalion, 3rd Special Forces Group (Airborne).

COL Henry is command surgeon for the United States Army Special Forces Command (Airborne), Fort Bragg, NC. COL Henry was awarded a Doctorate of Medicine degree from Howard University College of Medicine, Washington, DC in 1998. He was assigned a Transitional Internship at Tripler Army Medical Center, Honolulu, HI. He later completed his Family Medicine residency at DeWitt Army Community Hospital, Fort Belvoir, VA in 2004. His Medical Corps assignments included Flight Surgeon 1st Battalion, 10th Aviation Regiment (Bosnia), Brigade Surgeon Aviation Brigade and 1st Brigade/Task Force Falcon (Kosovo), 10th Mountain Division (Light); Brigade Surgeon 1st BCT, 101st Airborne Division (Air Assault), Fort Campbell, KY; Officer in Charge Clark and Pope Health Clinic, Womack Army Medical Center, Fort

Bragg, NC; and the Group Surgeon 3rd Special Forces Group, Fort Bragg, NC. His combat tours include OPERATION IRAQI FREEDOM as the 1st Brigade Combat Team Surgeon, Kirkuk, Iraq in 2006 and the deputy commander for Clinical Services 10th Combat Support Hospital, Ibn Sina Hospital, Baghdad, Iraq in 2009. He deployed in 2011 in support of OPERATION ENDURING FREEDOM, Afghanistan as the Combined Joint Special Operations Task Force – Afghanistan command surgeon.

Dr. Berry-Cabán is an epidemiologist at Womack Army Medical Center who earned his doctorate degree from the University of Wisconsin-Milwaukee. His background includes global health with medical and research missions to equatorial West Africa and Southeast Asia. He precepts Preventive Medicine in the Family Medicine residency program and is extensively published.

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