The Journal of Foot & Ankle Surgery 55 (2016) 117–120

Contents lists available at ScienceDirect

The Journal of Foot & Ankle Surgery

journal homepage: www.jfas.org

Association of Vitamin D With Stress Fractures: A Retrospective Cohort Study

Jason R. Miller, DPM, FACFAS [1], Karl W. Dunn, DPM, AACFAS [2], Louis J. Ciliberti Jr., DPM, AACFAS [3], Rikhil D. Patel, DPM [4], Brock A. Swanson, DPM [5]

[1] Fellowship Director, Pennsylvania Intensive Lower Extremity Fellowship, Premier Orthopaedics and Sports Medicine, Malvern, PA
[2] Fellow, Pennsylvania Intensive Lower Extremity Fellowship, Premier Orthopaedics and Sports Medicine, Malvern, PA
[3] Private Practice, Premier Orthopaedics and Sports Medicine, Malvern, PA
[4] Resident, Phoenixville Hospital Podiatric Surgical Residency, Phoenixville, PA
[5] Resident, Bryn Mawr Hospital Podiatric Surgical Residency, Bryn Mawr, PA

ARTICLE INFO

Level of Clinical Evidence: 3

Keywords:
bone health
deficiency
fatigue fracture
hypovitaminosis D
insufficiency
march fracture
supplementation

ABSTRACT

Vitamin D is an essential, fat-soluble nutrient that is a key modulator of bone health. Despite the gaining popularity throughout published medical studies, no consensus has been reached regarding a serum vitamin D level that will guarantee adequate skeletal health in a patient with an increased functional demand. The purpose of the present investigation was to examine the serum concentrations of vitamin D in patients with confirmed stress fractures. A total of 124 patients were included in our retrospective cohort study. Of the 124 patients, 53 had vitamin D levels measured within 3 months of diagnosis. An association was seen in patients with a stress fracture and vitamin D level measured, as 44 (83.02%) of the 53 patients had a serum 25-hydroxyvitamin D level <40 ng/mL. Although an association was seen at our institution in patients with stress fractures and a serum vitamin D concentration <40 ng/mL, a larger and prospective investigation is warranted to further understand the effect of vitamin D level and stress fracture prevention in an active, nonmilitary population.

The role of vitamin D in the body has recently become a subject of increasing interest in current medical studies owing to its many physiologic effects throughout multiple organ systems. In brief, vitamin D is an essential nutrient that can behave as a hormone that is obtained through diet and cutaneous synthesis by ultraviolet B radiation (1–4). Vitamin D has been linked to effects on mood and behavior, innate and acquired immune responses, metabolic function, and individually affecting the pancreas, heart, parathyroid, and skeletal muscles (1,2).

The primary physiologic function of vitamin D and its activated metabolites is to maintain serum calcium and phosphorus levels and to support bone mineralization and turnover (1,3). Vitamin D is essential for bone development and remodeling, as demonstrated by a direct correlation with rickets in children (3). Furthermore, a significant correlation has also been shown with adequate vitamin D and appropriate bone mass density. In contrast, it has been reported that hypovitaminosis D can lead to osteoporosis, osteomalacia, decreased bone mineral density, and, subsequently, the risk of acute fracture (4–8). Vitamin D insufficiency has been associated with increased age, obesity, female gender, geographic region and season predilection, pregnancy and lactation, and malabsorption syndromes (7,9).

Less known is the quantitative importance of vitamin D concentrations in the delicate balance of bone turnover and healing in the context of osseous loading and physiological stresses. The goal of the present investigation was to examine the serum concentrations of vitamin D in patients with confirmed stress fractures. By assessing the average serum vitamin D concentrations of those with stress fractures and evaluating the prevalence of deficiency or insufficiency according to the current guidelines, we wish to encourage a discussion of the possibility that a higher "norm" concentration of serum vitamin D should be recommended for active patients who may be at risk of stress fractures.

Patients and Methods

A single-center, retrospective medical record review was performed from the senior authors' (J.R.M., L.J.C.) practice during a 3-year period (July 31, 2011 to August 1, 2014). All patients who initially presented with lower extremity pain, with a suspected

Financial Disclosure: None reported.
Conflict of Interest: None reported.
Address correspondence to: Karl W. Dunn, DPM, AACFAS, Pennsylvania Intensive Lower Extremity Fellowship, Premier Orthopaedics and Sports Medicine, 266 Lancaster Avenue, Suite 200, Barr Building, Malvern, PA 19355.
E-mail address: dr.karldunn@gmail.com (K.W. Dunn).

1067-2516/$ - see front matter © 2016 by the American College of Foot and Ankle Surgeons. All rights reserved.
http://dx.doi.org/10.1053/j.jfas.2015.08.002

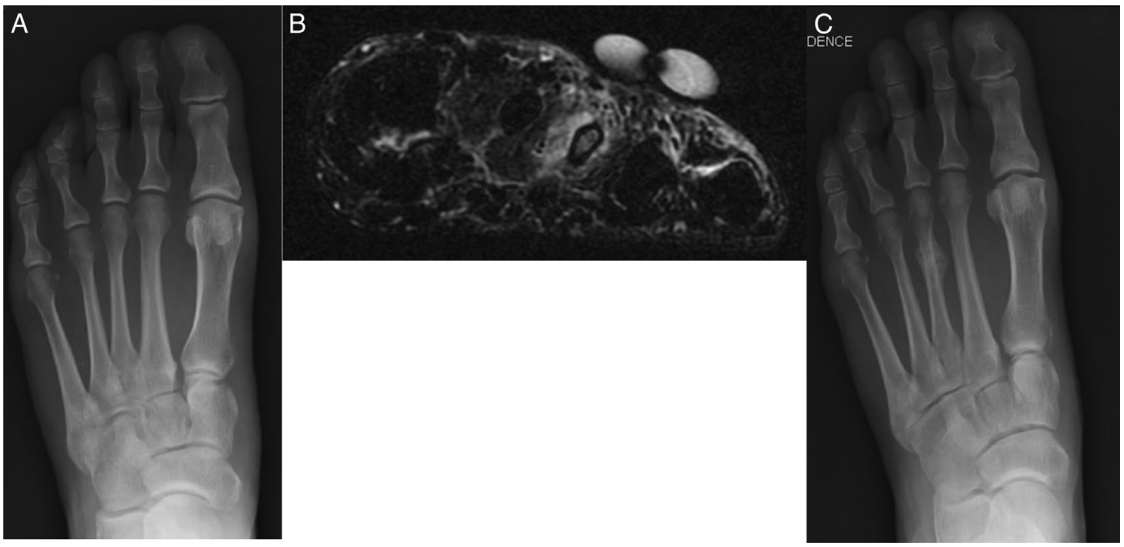

Fig. 1. A 51-year-old female presented with forefoot pain associated with weightbearing. The initial radiograph (*A*) did not display an acute fracture. The patient underwent subsequent magnetic resonance imaging (*B*), in which an increased signal in the bone marrow of the third metatarsal and surrounding soft tissues, consistent with a stress fracture, was seen on T_2-weighted and short T_1-weighted inversion recovery images (shown on coronal T_2-weighted images). The patient's serum 25-hydroxyvitamin D level was 33 ng/mL, and she was prescribed vitamin D_3 4000 IU daily. A follow-up radiograph (*C*) displayed circumferential callus formation after the patient had been placed in a fixed-walking boot for 6 weeks.

stress fracture, underwent plain film radiographs of the affected extremity. The patients were then sent for magnetic resonance imaging (MRI) for a confirmatory diagnosis if no acute fracture was seen, yet concern for the presence of a stress fracture remained based on the physical examination findings (Fig. 1). Musculoskeletal radiologists independently reviewed all the MRI scans, and the senior authors (J.R.M., L.J.C.) confirmed the diagnosis of a stress fracture after a review of the images based on an MRI (short T_1-weighted inversion recovery and T_2-weighted images) sequence displaying a high-signal intensity of the bone marrow (bone marrow edema) and the adjacent soft tissues.

The following clinical data were obtained from the private practice electronic database of the senior authors (J.R.M., L.J.C.): patient age, gender, body mass index, location of stress fracture, serum 25-hydroxyvitamin D [25(OH)D] levels within 3 months of the positive MRI diagnosis. The data identified were recorded and statistically analyzed for the investigation by 1 of us (K.W.D.), using the "International Classification of Diseases, version 9," codes 733.93, 733.94, and 733.95. All the patients with a positive diagnosis of an acute stress fracture from the MRI findings were included in the present study, for a total of 124 consecutive patients. No patient was excluded from the present study once a diagnosis of a stress fracture had been confirmed and supported by the electronic medical record data.

Results

Of the 124 patients, 42 (33.9%) were male and 82 (66.1%) were female. Their mean age was 43.92 ± 17.47 years, and the mean body mass index of those with it recorded (120 [96.8%] of 124 patients) was 26.81 ± 6.30 kg/m^2. The most common bone with a stress fracture was the second metatarsal (n = 42 [33.9%]), followed by the third metatarsal (n = 22 [17.7%]). The stress fracture anatomic locations are presented in Fig. 2. The serum 25(OH)D level was recorded within 3 months of diagnosis for 53 (42.74%) of the 124 patients. The mean serum 25(OH)D of all patients was 31.14 ± 14.71 ng/mL. Similar serum levels were reported for the males (31.0 ± 15.66 ng/mL) and females (31.21 ± 14.23 ng/mL) (Mann-Whitney U test p value = .58).

Using the standards recommended by the Vitamin D Council (San Luis Obispo, CA; sufficient range 40 to 80 ng/mL; Fig. 3), 44 (83.02%) of the 53 patients would have been classified as having insufficient or deficient vitamin D levels. According to the standards set by the Endocrine Society (Washington, DC; sufficient range 30 to 100 ng/mL), 28 (52.83%) of the 53 patients would have been classified as having insufficient or deficient vitamin D levels.

Discussion

An individual's vitamin D concentration is intimately linked to the absorption of dietary calcium and phosphorus. In a vitamin D-deficient state, only 10% to 15% of dietary calcium and 50% to 60% of dietary phosphorus will be absorbed. Thus, a decrease occurs in the serum-ionized calcium levels. This is recognized by the calcium sensor in the parathyroid glands, resulting in an increase in the secretion of parathyroid hormone. In turn, parathyroid hormone enhances the expression of RANKL on osteoblasts to increase the production of mature osteoclasts to mobilize skeletal calcium stores (3). Thus, a decrease in bone mineralization and structural integrity can develop.

Although several guidelines have been published to determine the vitamin D status, the current thresholds are considered estimates, which were largely observationally and determined from the occurrence of secondary hyperparathyroidism in vitamin D deficiency through the use of serum parathyroid hormone levels as a surrogate parameter for the optimal 25(OH)D serum level. Furthermore, no minimum 25(OH)D serum level has been defined that can guarantee adequate skeletal health in a patient with an increased functional demand (10).

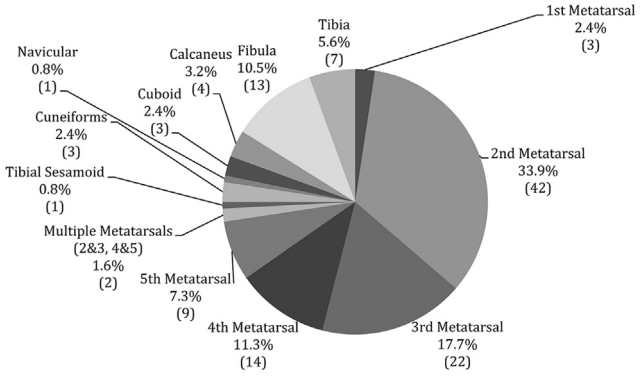

Fig. 2. Anatomic location of stress fractures (N = 124 patients).

	Vitamin D Council	Endocrine Society
Deficient	0-30 ng/mL	0-20 ng/ mL
Insufficient	31-39 ng/mL	21-29 ng/mL
Sufficient	40-80 ng/ mL	30-100 ng/ mL
Toxic	>150 ng/ mL	

Fig. 3. Current recommendations for serum 25-hydroxyvitamin D [25(OH)D] levels from the Vitamin D Council and Endocrine Society.

The association between serum 25(OH)D levels and the occurrence of stress fractures has been previously documented in published studies, extensive investigation has been performed and association has been reported in young and active military recruits (11). In a randomized, double-blind, placebo-controlled trial of female military recruits, the addition of 2000 mg of calcium and 800 IU of vitamin D demonstrated a 20% reduction in stress fracture incidence (12). In a recent report using a histomorphometric bone analysis in autopsy specimens, the investigators strongly recommended a minimum of 30 ng/mL in conjunction with sufficient calcium intake to promote skeletal health (10). Other researchers have advocated a higher concentration of serum 25(OH)D. In a case-controlled study of 600 female Navy recruits, investigators found a twofold greater risk of stress fractures of the tibia and fibula in females with a vitamin D level of <20 ng/mL compared with females with concentrations >40 ng/mL. The investigators concluded that a serum vitamin D of ≥40 ng/mL was required for the prevention of stress fracture (13). Similar findings were seen throughout our data, with 44 (83.02%) of 53 patients having levels <40 ng/mL.

Therefore, we would recommend a serum 25(OH)D of ≥40 ng/mL would be optimal for stress fracture prophylaxis, especially for active patients with a moderate or high functional demand. In our cohort, 9 (16.98%) of 53 patients were recorded to have a serum 25(OH)D level >40 ng/mL, indicating that vitamin D is not the sole predictor in the occurrence of a stress fracture. Other factors, including white race, female gender, nicotine and alcohol abuse, steroid use, low bone density, low body mass index, and bisphosphonate therapy have all shown correlations with the development of stress fractures (9). Patients who regularly exercise or enjoy participating in higher impact activities should be advised on proper and gradual training regimens to reduce the risk of the development of a stress fracture.

When a vitamin D insufficiency or deficiency has been diagnosed in the context of a stress fracture, vitamin D supplementation should be implemented to improve the body's osseous healing capability. Current data have shown that 100 IU daily of vitamin D_3 increases vitamin D blood levels by 1 ng/mL during a 2- to 3-month span (14). The Endocrine Society has suggested that adults with vitamin D deficiency, regardless of the presence of a stress fracture, should supplement with 50,000 IU of vitamin D_2 or vitamin D_3 once a week for 8 weeks or its equivalent of 6000 IU daily to achieve a 25(OH)D level >30 ng/mL (15). As such, we would advocate high dosage supplementation for individuals with a 25(OH)D of <35 ng/mL, introducing a 4- to 8-week regimen of a 50,000 IU weekly dose until fracture healing has occurred. For those with a serum concentration of 35 to 40 ng/mL, we would recommend 3000 to 5000 IU daily. Repeat serum 25(OH)D measurements should be taken every 3 months or after the patient's treatment course. If adequate levels have been met, the patient should be advised to continue with a lower maintenance supplementation dose of ≥2000 IU daily to prevent the recurrence of a stress fracture. Although supplementation of vitamin D in these dosages has shown safety, with virtually no associated risk of toxicity throughout several reviews (14–16), long-term management and physician referral might be indicated for some individuals.

A major strength of the present study was the association of patients with stress fractures and a serum 25(OH)D level <40 ng/mL. Agreement between the results of the present study and previous recommendations was seen in that a minimum concentration of 40 ng/mL should be achieved in active individuals to protect against stress fractures (13,17). However, the present study had some inherent limitations. First, this was a retrospective analysis of a small sample size of patients without a control group. Second, 53 (42.74%) of the 124 patients who had developed a stress fracture had had the serum 25(OH)D level measured within 3 months of the stress fracture diagnosis, indicating a possible selection bias, although a number of patients who were sent for laboratory testing refused it. Some of the patients who were already supplementing with vitamin D (≤2000 IU daily) either by a physician's orders or on their own accord were still advised to have the serum 25(OH)D level measured. These patients were generally less likely to have had the blood test performed. Of those who did participate in laboratory testing, the serum 25(OH)D measured <30 ng/mL in some patients despite their previous supplementation. These patients were then prescribed an increased dosage. Regardless of previous supplementation, we would advocate that the serum 25(OH)D level be measured whenever a stress fracture is encountered to rule out the possibility of lingering vitamin D deficiency or insufficiency. Third, the activity level among the present cohort was not quantified, because incomplete documentation was encountered during our retrospective review regarding the patients' workout regimens and so forth. A larger, prospective investigation is warranted to gain further information regarding the impact of vitamin D supplementation and stress fracture prevention in a nonmilitary population.

In conclusion, an association was seen in patients with stress fractures and a serum 25(OH)D level <40 ng/mL. Greater than previously understood serum concentrations of vitamin D might be necessary to prevent stress fractures in active individuals.

References

1. Yoshida T, Stern PH. How vitamin D works on bone. Endocrinol Metab Clin North Am 41:557–569, 2012.
2. Lamberg-Allardt C, Brustad M, Meyer HE, Steingrimsdottir L. Vitamin D—a systematic literature review for the 5th edition of the Nordic nutrition recommendations. Food Nutr Res 57:226–271, 2013.
3. Holick MF. Resurrection of vitamin D deficiency and rickets. J Clin Invest 116:2062–2072, 2006.
4. Bikle DD. Vitamin D and bone. Curr Osteoporos Rep 10:151–159, 2012.
5. Glendenning P, Inderjeeth CA. Vitamin D: Methods of 25 hydroxyvitamin D analysis, targeting at risk populations and selecting thresholds of treatment. Clin Biochem 45:901–906, 2012.
6. Bischoff-Ferrari H. Vitamin D—from essentiality to functionality. Int J Vitam Nutr Res 82:321–326, 2012.
7. Rizzoli R, Boonen S, Brandi ML, Bruyere O, Cooper C, Kanis JA, Kaufman JM, Ringe JD, Weryha G, Reginster JY. Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Curr Med Res Opin 29:305–313, 2013.
8. Ceroni D, Anderson de la Llana R, Martin X, Lamah L, De Coulon G, Turcot K, Dubois-Ferriere V. Prevalence of vitamin D insufficiency in Swiss teenagers with appendicular fractures: a prospective study of 100 cases. J Child Orthop 6:497–503, 2012.
9. Breer S, Krause M, Marshall RP, Oheim R, Amling M, Barvencik F. Stress fractures in elderly patients. Int Orthop 36:2581–2587, 2012.
10. Priemel M, von Domarus C, Klatte TO, Kessler S, Schlie J, Meier S, Proksch N, Pastor F, Netter C, Streichert T, Puschel K, Amling M. Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. J Bone Miner Res 25:305–312, 2010.

11. Dao D, Sodhi S, Tabasinejad R, Peterson D, Ayeni OR, Bhandari M, Farrokhyar F. Serum 25-hydroxyvitamin D levels and stress fractures in military personnel. Am J Sports Med 43:2064–2072, 2015.
12. Lappe J, Cullen D, Haynatzki G, Recker R, Ahif R, Thompson K. Calcium and vitamin D supplementation decreases incidence of stress fracture in female navy recruits. J Bone Miner Res 23:741–749, 2008.
13. Burgi AA, Gorham ED, Garland CF, Mohr SB, Garland FC, Zeng K, Thompson K, Lappe JM. High serum 25-hydroxyvitamin D is associated with a low incidence of stress fractures. J Bone Miner Res 26:2371–2377, 2011.
14. Prentice A. What are the dietary requirements for calcium and vitamin D. Calcif Tissue Int 70:83–88, 2002.
15. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 96:1911–1930, 2011.
16. Tarushkin V, Bender A, Psaty EL, Engelsen O, Wang SQ, Halpern AC. Estimated equivalency of vitamin D production from natural sun exposure versus oral vitamin D supplementation across seasons at two US latitudes. J Am Acad of Dermatol 62:929.e1–929.e9, 2010.
17. The Vitamin D Council. Testing for vitamin D. Available at: http://www.vitamindcouncil.org/about-vitamin-d/testing-for-vitamin-d/#. Accessed September 2, 2014.