Surgical Considerations for Vitamin D Deficiency in Foot and Ankle Surgery

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KEYWORDS

• Vitamin D • Deficiency • Hypovitaminosis D • Bone marrow edema syndrome (BMES)
• Foot and ankle

KEY POINTS

- A substantial percentage of patients undergoing foot and ankle surgery are vitamin D deficient.
- Consideration should be given for preoperative vitamin D testing in at-risk patients undergoing foot and ankle surgery.
- Vitamin D repletion either preoperatively or postoperatively is a proposed way to optimize outcomes in orthopedic surgery, including foot and ankle surgery.
- There may be a correlation between vitamin D deficiency and poor clinical outcomes.
- Vitamin D supplementation is relatively safe and inexpensive.

INTRODUCTION

Vitamin D deficiency is extremely common, affecting more than one billion people worldwide.[1] There are many known causes of vitamin D deficiency, including malnutrition, malabsorption syndromes, and inadequate sun exposure. Vitamin D level has been shown to correlate to both climate and geography, which is in part thought to be due to variations in sunlight, which affects vitamin D metabolism (Fig. 1).[2,3] Vitamin D deficiency is particularly prevalent in certain populations. For example, patients with darker skin living in areas with less sun exposure are at particular risk for low vitamin D.[1,3,4] Certain medical conditions also predispose to vitamin D deficiency, including patients with gastrointestinal malabsorption syndromes and renal insufficiency.[1]

Relating to orthopedics, certain patient subgroups have been noted to be at particular risk for low vitamin D levels. These subgroups include orthopedic trauma patients,[5–11] geriatric hip and fragility fracture patients,[12–15] patients undergoing joint replacement surgery,[16–25] spinal fusion patients,[26–28] those undergoing scoliosis correction,[29] and patients with foot and ankle conditions.[30–35] This article summarizes the current literature regarding vitamin D deficiency in patients undergoing orthopedic surgery, focusing on patients with foot and ankle conditions.

VITAMIN D METABOLISM

A general understanding of vitamin D metabolism is necessary to appreciate the intricate relationship between vitamin D levels, calcium homeostasis, and bone health (see Fig. 1). Vitamin D is absorbed both through the skin and through the gastrointestinal tract. Vitamin D2, also known as ergocalciferol, is derived from plant sources and generated by UV

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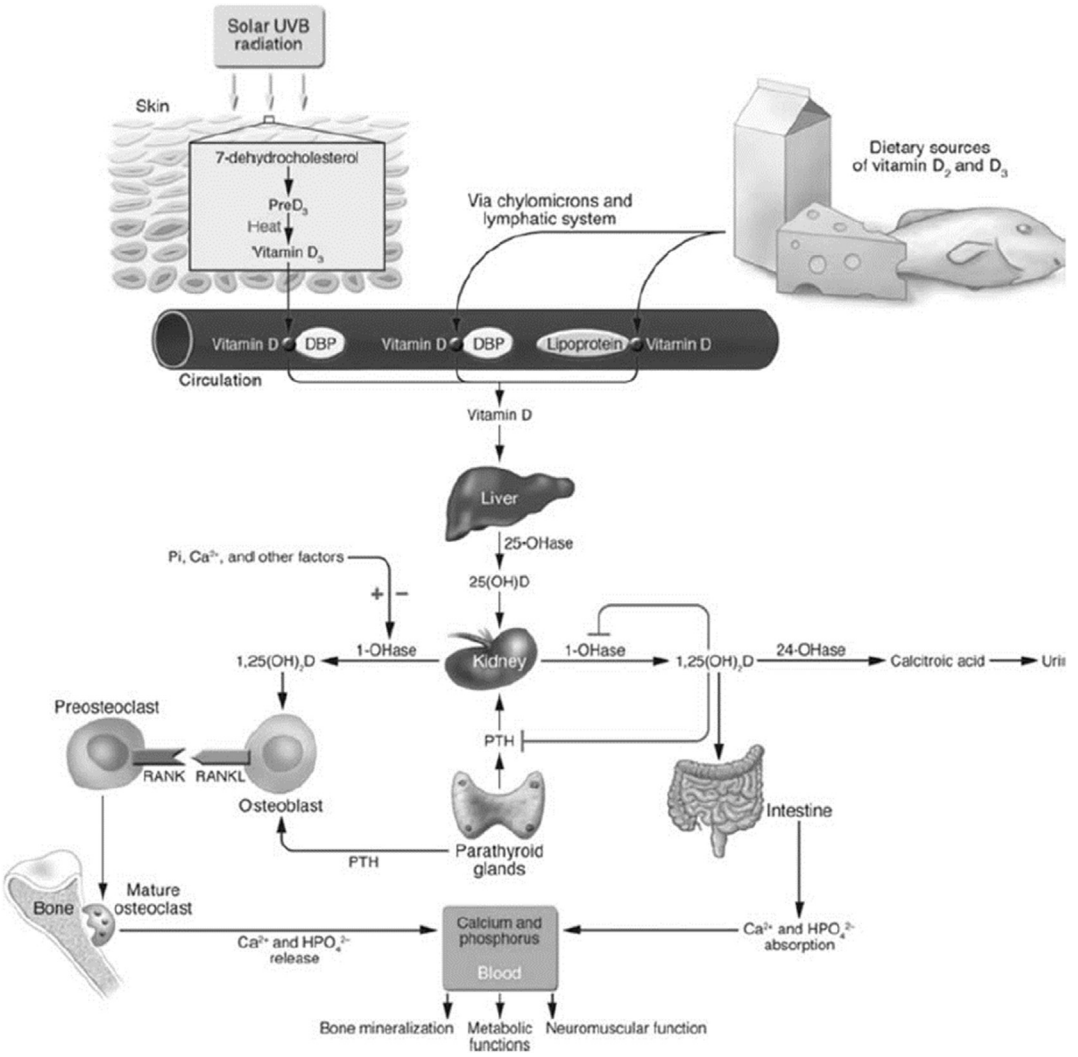

Fig. 1. Photoproduction and metabolism of vitamin D and the various biologic effects of 1,25(OH)2D on calcium, phosphorus, and bone metabolism. DBP, Vitamin D Binding Protein. (*From* McCabe MP, Smyth MP, Richardson DR. Current concept review: vitamin D and stress fractures. Foot Ankle Int 2012;33(6):527; with permission.)

radiation of ergosterol from yeast.[1] Vitamin D3 is called cholecalciferol and is generated from the UV irradiation of 7-dehydrocholesterol from lanolin, which is found in animals.[1,36] Both vitamin D2 and vitamin D3 are converted to 25-hydroxyvitamin D (25(OH)D) in the liver. This major circulating metabolite, also called calcidiol, is the most commonly measured vitamin D laboratory value.

Calcidiol (25(OH)D) circulates in the blood and undergoes hydroxylation in the kidneys to become calcitriol (1,25(OH)D).[1,36] As the active form of vitamin D, calcitriol affects both bone turnover and gastrointestinal absorption to regulate calcium and phosphate levels. In the setting of vitamin D deficiency, less calcium is absorbed from the gastrointestinal track, which upregulates parathyroid hormone (PTH).[1,37,38] Increased PTH has the effect of increasing bone resorption, which can lead to osteoporosis, osteomalacia/rickets, and compromised bone healing.[1,39]

VITAMIN D AND MUSCULOSKELETAL HEALTH

Vitamin D levels are reported in either nanograms per milliliter or nanomoles per liter. Calcidiol (25(OH)D) is the value measured in most routine laboratory tests. Although there is no universally accepted classification of vitamin D deficiency or insufficiency, there is a consensus

in the literature regarding normal values. The Endocrine Society defines vitamin D insufficiency as between 20 and 30 ng/mL and vitamin D deficiency as less than 20 ng/mL.[40] Patients with values greater than 30 ng/mL are considered sufficient (Table 1). Most of the studies in the orthopedic and foot and ankle literature use the Endocrine Society definition of vitamin D adequacy, and unless otherwise noted, all articles referenced in this chapter use this definition.

Vitamin D is critical to bone health due to its regulation of serum calcium and phosphate. In the most basic sense, low levels of vitamin D result in low levels of calcium. In one of the most striking examples of vitamin D deficiency, rickets, bone is exceptionally soft and weakened, which results in delayed growth and skeletal deformity.[1,3,39] In cases of renal osteodystrophy, effective vitamin D deficiency results in substantial bone weakness and fracture risk.[1,37] These examples illustrate the integral role that vitamin D plays in bone health. Similarly, low vitamin D has been identified as a common cause of fragility fractures in patients without known medical underlying risk factors for vitamin D deficiency.[12–14,41] Fragility fractures are not only an enormous burden to the elderly population, in which they most commonly occur, but also an economic burden to the health care system.[1,42]

In addition to the well-documented effects of vitamin D on bone homeostasis, vitamin D also directly affects muscle. Adequate vitamin D levels have been associated with minimizing risks of falls, suggesting a connection between vitamin D and muscle strength.[1,43,44] Vitamin D interacts directly with muscle through the vitamin D receptor that is found in skeletal muscle.[43,45,46] Additional research is needed to fully elucidate the role of vitamin D and skeletal muscle health and function.

For supplementation in those with adequate vitamin D levels, the Endocrine Society Clinical Practice Guidelines recommend at least 600 IU of vitamin D daily for patients age 1 to 70 and at least 800 IU daily for patients over the age of 70, with a general upper limit of 4000 IU daily for adults.[40,47] For those found to be deficient of vitamin D, it is recommended that children aged 1 to 18 take 2000 IU daily or a 6-week course of 50,000 IU weekly followed by 400 to 1000 IU daily.[40] Adults with deficiency are recommended 6000 IU daily or 50,000 IU weekly for 8 weeks followed by maintenance treatment of 1500 to 2000 IUs daily.[40] The goal of treatment is to maintain levels greater than 30 ng/mL. Either D2 or D3 supplementation is acceptable.[40]

Vitamin D toxicity has been described and is extremely rare. Levels greater than 150 ng/mL are considered excessive and can result in intoxication.[48] Symptoms of vitamin D intoxication range from mild gastrointestinal distress (nausea, vomiting, and diarrhea) to more severe symptoms, including lethargy, headache, cardiac arrhythmia, muscle and joint pain, frequent urination, and kidney stones.[48,49]

Table 1
Normal 25-hydroxyvitamin D values and cutoffs for insufficiency and deficiency

Diagnosis	Values (ng/mL)	Values (nmol/L)
Sufficient	>30	>75
Insufficient	21–29	52.5–72.5
Deficient	<20	<50

VITAMIN D IN ORTHOPEDIC TRAUMA

The rate of vitamin D deficiency is particularly high in orthopedic trauma patients, including both low-energy and high-energy trauma.[7,10,11,13,41] In the geriatric hip fracture population, vitamin D levels have been reported to be as high as 76%.[13] Nevertheless, despite high rates of deficiency among those with fractures, it is not clear that vitamin D deficiency affects outcomes after fracture. A recent meta-analysis evaluated vitamin D supplementation in fracture patients and found that vitamin D supplementation was a safe way to increase vitamin D levels in all cases, but it was not clear whether supplementation affected outcomes.[9] Similarly, a study from Singapore did not show any effect of vitamin D deficiency on clinical outcomes in 171 patients with geriatric hip fractures.[15] Lee and colleagues[13] in 2015 looked at vitamin D deficiency as a risk factor for mortality in older patients with a hip fracture and found no correlation between serum 25(OH)D levels and mortality. Although vitamin D levels may not affect clinical outcomes after trauma, some researchers think that vitamin D has an important role in fracture prevention. A large meta-analysis published in 2005 concluded that vitamin D supplementation (700–800 IU daily) reduced the risk of hip and any nonvertebral fractures in ambulatory or institutionalized elderly patients.[50]

Nonunions in trauma patients have been linked to vitamin D deficiency. In 2007, Brinker and colleagues[5] investigated 683 patients who developed a nonunion from a fracture over a 7-year period. The investigators identified patients in whom a metabolic cause for nonunion was suspected by identifying those with adequate fracture stabilization and reduction, those who had a history of multiple low-energy fractures, and those with a

nonunited pubic rami or sacral ala fracture. Thirty-seven patients were identified and referred to an endocrinologist. Of these, 68% were found to be vitamin D deficient. Although this study does not definitively identify a causal link between low vitamin D levels and the development of nonunion, most patients deemed to be at highest risk for nonunion had vitamin D deficiency.

The orthopedic trauma literature also sheds light on the effectiveness of vitamin D supplementation in patients with vitamin D deficiency. In 2015, Robertson and colleagues[8] monitored vitamin D levels of 201 orthopedic trauma patients throughout the course of treatment. Before initiation of vitamin D therapy, the rate of vitamin D deficiency was 40% and the rate of insufficiency was 44%. All patients, regardless of preoperative levels, received 1000 IU D3 and 1500 mg of calcium daily, and those insufficient or deficient additionally received 50,000 IU D2 weekly for 8 weeks. Vitamin D levels in all patients improved throughout follow-up, but most patients did not normalize. These data suggest that supplementation can improve vitamin D levels, although attention should be given to dosing and duration of supplementation.

VITAMIN D IN ELECTIVE ORTHOPEDIC SURGERY

Vitamin D deficiency has been reported to be present in up to 86% of patients undergoing elective orthopedic procedures.[16,18,27,28,31,51,52] Patients undergoing elective hip and knee replacement have been found to have a particularly high prevalence of vitamin D deficiency.[16,22] For comparison, although rates of vitamin D deficiency tend to vary geographically, an analysis of healthy adults aged 18 to 29 in the United States reported 36% had 25(OH)D levels less than or equal to 20 ng/mL.[53,54] A study of healthy patients in France reported a deficiency rate of 14%.[55] Although these groups vary in terms of age, many studies evaluating elective orthopedic patients report substantially higher rates of deficiency than population norms.

Studies have shown that patients with lower preoperative vitamin D levels have lower preoperative functional status.[21] Whether this is due to a causal effect of vitamin D or is representative of poorer general fitness is uncertain. Studies also suggest that patients with lower vitamin D levels have lower outcome scores after total knee and hip replacement.[23,24,56] Shin and colleagues[24] analyzed a prospective cohort of 92 patients who underwent total knee arthroplasty and found that mean postoperative Knee Society Scores and additional performance tests were significantly lower in the vitamin D deficient group. Unnanuntana and colleagues[25] showed that early postoperative functional outcomes, at 6 weeks, were similar in patients who were deficient versus sufficient preoperatively, as long as adequate vitamin D supplementation was begun as soon as it was identified. Additional research is needed to fully elucidate the effects of vitamin D deficiency and supplementation in the arthroplasty population.

There also appears to be a link between vitamin D and periprosthetic infection rate, length of hospital stay, and overall complication rates after elective orthopedic surgery.[17,19,20,22] Hegde and colleagues[17] evaluated 6598 patients undergoing elective joint replacement in the Humana registry and found those with vitamin D deficiency to have a statistically higher rate of periprosthetic surgical site infection and prosthesis explantation as well as a higher overall complication rate. Similarly, Maier and colleagues[19] found significant differences in vitamin D levels in patients who developed an infection after hip, knee, or shoulder arthroplasty when compared with patients who were either scheduled for arthroplasty or developed aseptic loosening. Maier and colleagues[20] also reported longer hospital stays in those with vitamin D deficiency in 1083 patients undergoing elective hip or knee arthroplasty.

VITAMIN D IN FOOT AND ANKLE SURGERY

Much of the early literature looking at hypovitaminosis D and foot and ankle patients relates to bone marrow edema syndrome, also known as transient osteoporosis.[57] Bone marrow edema syndrome is characterized by a sudden onset of severe periarticular pain without trauma and has a predilection for the lower extremities, including the hip, knee, foot, and ankle.[57,58] Multiple studies have evaluated the association between vitamin D and bone marrow edema syndrome in the foot and have found vitamin D deficiency in 84% to 90% of these patients.[57,59,60] Treatment of bone marrow edema syndrome is largely nonsurgical and includes off-loading, synthetic prostacyclin analogues, bisphosphonates, and vitamin D supplementation.[57] When combined with other medical therapies, such as bisphosphonates, vitamin D supplementation seems to cause some improvement in pain, suggesting vitamin D supplementation may be an important part of treatment of these patients.[59–61]

More recently, studies have examined rates of hypovitaminosis D in patients with foot and

ankle injuries (Table 2). In 2014, Smith and colleagues[33] evaluated the prevalence of vitamin D deficiency in patients who presented with acute low-energy foot and ankle injuries. The study cohort included patients with a low-energy ankle fracture, fifth metatarsal base fracture, or stress fracture of the foot and ankle. A group of patients with an ankle sprain were used as a control. Of patients with a low-energy foot or ankle fracture, 47% were vitamin D insufficient, with 13% of patients severely deficient. These values were statistically significantly lower than in the control group, of which 71% had normal vitamin D levels. Further analysis revealed an association between low vitamin D and smoking, obesity, and other medical risk factors for hypovitaminosis D. This study demonstrated that vitamin D deficiency is particularly common among patients with a low-energy fracture of the foot or ankle. Although foot and ankle injuries are not typically classified as fragility fractures, the investigators suggest that clinicians consider these injuries to be related to overall bone health. Accordingly, consideration should be given to checking vitamin D levels in patients who present with low-energy foot or ankle injuries.

Vitamin D levels have also been evaluated in elective foot and ankle surgery populations. A study published in 2017 evaluated 577 patients in England undergoing elective foot and ankle surgery.[30] This large cohort reported the levels of vitamin D to be normally distributed, yet with only 18% of patients within the normal range. The investigators noted an association between the season and vitamin D levels, which can likely be attributed to levels of sun exposure.

In 2016, Michelson and colleagues[31] looked at a series of 81 patients undergoing ankle, hindfoot, or midfoot arthrodesis. Within this cohort,

Table 2
Summary of studies evaluating foot and ankle conditions and vitamin D

Authors	Level of Evidence	Major Conclusions
Bogunovic et al,[52] 2010	Retrospective review	Inadequate vitamin D levels were found in 34% of 192 patients who underwent foot and ankle surgery, of which 32% were deficient
Smith et al,[33] 2014	Prospective case control	Vitamin D insufficiency was found in 47% of patients with foot and ankle injuries, of which in 13% were deficient. Vitamin D values were lower in patients with a fracture compared with patients with a sprain
Michelson et al,[31] 2016	Prospective study	Hypovitaminosis D was found in 67% of 118 patients undergoing elective ankle, hindfoot, or midfoot arthrodesis
Warner et al,[35] 2016	Retrospective review of prospective patient registry	Vitamin D insufficiency was present in 32% of patients operatively treated for ankle fracture, and vitamin D deficiency was present in 37%. Patients with vitamin D deficiency had worse FAOS scores in some domains than those who with levels greater than 20 ng/mL
Aujla et al,[30] 2017	Prospective cohort	Hypovitaminosis D was present in 83% of a total of 577 patients undergoing elective foot and ankle surgery
Moore et al,[32] 2017	Retrospective case control	Hypovitaminosis D was present in 48% of patients who developed a nonunion after elective foot and ankle reconstruction compared with 10% of patients who underwent successful fusion
Telleria et al,[34] 2018	Comparative study	Hypovitaminosis D was identified in 54% of patients with an osteochondral lesion of the talus compared with 28% of patients with an ankle sprain

67% of patients were found to have low vitamin D levels (<30 ng/mL). Interestingly, older patients had a statistically lower risk for hypovitaminosis D. The investigators also looked at the Charlson Co-Morbidity Index.[62] Patients with a Charlson Co-Morbidity Index greater than or equal to 3, which corresponds to either patients with diabetes or multiple comorbid conditions, were at increased risk for vitamin D deficiency. To address the deficiency, all patients were placed on 2000 IU D3 and 750 mg calcium carbonate daily and those with hypovitaminosis D were also treated with 50,000 IU D2 three times a week for 2 to 3 months. Despite this repletion, only 56% of patients who were deficient corrected to normal levels. This study illustrates 2 important points. The prevalence of vitamin D deficiency in patients undergoing foot and ankle fusions, at least in Vermont, is quite high. Second, the repletion approach used in this study failed to adequately normalize levels in many patients.

An additional group of patients who have been recently studied are those with osteochondral lesions of the talus (OLTs). Patients with OLTs have a particularly high rate of vitamin D deficiency, as identified by Telleria and colleagues.[34] In patients with a documented OLT, the prevalence of vitamin D insufficiency is 54%. This rate of hypovitaminosis contrasts with an acute ankle sprain. These data suggest that OLTs may be related to an underlying bone abnormality, and the investigators suggest that patients presenting with a talar osteochondral lesion should be evaluated for vitamin D sufficiency. Although repletion was not evaluated in this study, the implication is that vitamin D and overall bone health should be considered when treating patients with OLT. Other studies have looked at juvenile osteochondritis dissecans and have similarly found high rates of vitamin D deficiency, ranging from 60% to 78%.[63,64]

The relationship between vitamin D deficiency and nonunion has also been studied in patients undergoing foot and ankle surgery.[32] Twenty-nine patients who underwent successful arthrodesis (forefoot, midfoot, hindfoot, ankle) were matched to 29 patients who developed a nonunion after an arthrodesis procedure. Vitamin D deficiency or insufficiency was identified in 48% of patients who developed a nonunion, compared with 10% in patients who united. Statistical analysis revealed that patients with a preoperative diagnosis of vitamin D insufficiency or deficiency were 8 times more likely to develop a nonunion than patients who had sufficient vitamin D levels. Although this study is small and cannot definitively link hypovitaminosis D and nonunion, these data suggest that an association may exist between vitamin D and the development of nonunion in foot and ankle surgery. Further study into these relationships is needed.

With respect to treatment of hypovitaminosis D, there are very few studies that examine the benefits of treatment on outcomes after foot and ankle surgery. In a study examining hypovitaminosis D in patients undergoing ankle fracture fixation, Warner and colleagues[35] reported improved outcomes in patients who were vitamin D sufficient. In this study, the investigators identified a hypovitaminosis D prevalence of 69% in a registry of 98 patients. Patients with vitamin D deficiency had statistically lower Foot and Ankle Outcome Score (FAOS), specifically in the symptoms and quality-of-life domains. Whether the poorer outcome was due to the vitamin D level or if this was an indication of poorer overall fitness is not known. If an association between vitamin D and outcomes does exist, one can theorize as to why vitamin D is beneficial. This benefit could be due to direct effects on bone healing or alternatively influencing balance and muscle strength and thus facilitating better rehabilitation and recovery.[43,65,66]

With respect to postoperative rehabilitation after foot and ankle surgery, vitamin D has been shown to benefit skeletal muscle and athletic performance. A recent review examines the role of vitamin D in muscle function.[43] Skeletal muscle has a vitamin D receptor that, once activated, enhances the interaction between myosin and actin. In a murine knockout model, mice without functional vitamin D receptors have been shown to have smaller muscle fiber size and body weight compared with normal mice, even when calcium levels are normalized.[43,67] Vitamin D is thus postulated to have a direct effect on muscle strength, performance, and recovery.[43,45] Additional research is necessary to further develop the understanding of the complex interplay between vitamin D and muscle strength, particularly as it pertains to recovery after injury or surgery.

SUMMARY

In summary, vitamin D deficiency is common in patients undergoing orthopedic procedures, including patients with foot and ankle conditions and those undergoing foot and ankle surgery. As the understanding and awareness of vitamin D and bone health evolve, we continue to identify conditions in which vitamin D

deficiency is clinically relevant. The limited data available to date suggest that patients who are vitamin D sufficient may have improved outcomes. The authors would thus recommend monitoring vitamin D levels as part of the preoperative evaluation for certain foot and ankle conditions. Because of its low cost and ease of administration, vitamin D optimization should be a routine consideration before orthopedic surgery.

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