Review

Vitamin D in Foot and Ankle Fracture Healing

A Literature Review and Research Design

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Abstract: *Vitamin D is a generic name for a group of essential vitamins, or secosteroids, important in calcium homeostasis and bone metabolism. Specifically, efficacy of vitamin D with regard to bone healing is in question. A literature review was performed, finding mostly large studies involving vitamin D effects on prevention of fractures and randomized animal model studies consisting of controlled fractures with vitamin D interventions. The prevention articles generally focus on at-risk populations, including menopausal women and osteoporotic patients, and also most often include calcium in the treatment group. Few studies look at vitamin D specifically. The animal model studies often focus more on vitamin D supplementation; however the results are still largely inconclusive. While recent case reports appear promising, the ambiguity of results on the topic of fracture healing suggests a need for more, higher level research. A novel study design is proposed to help determine the efficacy on vitamin D in fracture healing.*

Levels of Evidence: *Therapeutic, Level IV: Systematic Review*

Keywords: bone healing/orthobiologics; bone; trauma; general disorders; fractures; sprains; and strains; sports podiatry

Normal bone metabolism requires the maintenance of several molecules. Parathyroid hormone and vitamin D are regulated by the body to ensure tight management of both calcium and phosphate levels, as well as bone homeostasis. Vitamin D is obtained by both diet and metabolism from sunlight; it is one of a short list of endogenously created vitamins.[1] A fat-soluble vitamin, it is present in several forms. Ergocalciferol, vitamin D_2, is a slightly less active form, originating in nonanimal species, such as fungus and plants. When ingested, it is uncertain how much ergocalciferol can be converted to biologically active vitamin D in our bodies, though it is not thought to be an effective supplement.[2] The more active form of consumable vitamin D, vitamin D_3 or cholecalciferol, comes from animals. Produced in the skin of vertebrates, it is formed using ultraviolet radiation to become active. Vitamin D, as a whole, is also commonly deficient in several populations, including African Americans, Hispanics, those lacking college education, who were obese, are in poor health, suffer from hypertension, have low high-density lipoprotein levels, or who do not consume milk daily.[3] Deficiency in children is significant for leading to rickets, while a deficiency in adults leads to osteomalacia.

> "... there are few foot and ankle publications discussing the importance of vitamin D to lower extremity bone health, specifically in fracture healing."

It is hypothesized that low levels of vitamin D can lead to pathologic fractures. Several studies exist to corroborate this[4-11]; however, there are few foot and ankle publications discussing the importance of vitamin D

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to lower extremity bone health, specifically in fracture healing. Even though vitamin D is stored in and produced by the body, incidences of hypervitaminosis are rare, even at high supplemental dosages. As such, vitamin D can be considered a relatively safe dietary supplement. This literature review is meant to shed light on whether or not vitamin D supplementation is efficacious for the treatment of pedal fractures and postsurgical bone healing.

Normal Vitamin D Levels

Unlike most clinically obtained diagnostic values, the normal range of vitamin D is highly variable from laboratory to laboratory. There are several challenging aspects to accurately determining normal and pathologic levels. Seasonal variance due to sun exposure, nonstandardized testing, dietary intake, and even gender and age can have an effect on what a "normal range" would look like. Commonly, laboratories use the compound 25-hydroxycholecalcifrol, also known as calcidiol or 25(OH)D, as the measurement standard. Calcidiol is not the most active form in our body, though it is generally considered to be the best, most stable indicator of our vitamin D levels. Acting as a prehormone, calcidiol is converted to the active 1,25-dihydroxycholecalciferol, or calcitriol, in the kidney where it can begin to work on promoting dietary calcium absorption. The length of the half-life appears to be the major contributing factor as to which gets measured. Calcidiol levels are relatively stable, with a half-life of around 15 days, while calcitriol, of which levels are more important physiologically, only has a 15-hour half-life. That is to say someone who has chronically low vitamin D levels can occasionally have a normal calcitriol level.[12]

The US National Institutes of Health recommends calcidiol plasma levels of more than 30 nmol/L, less than which is termed deficiency, while they state that more than 50 nmol/L is sufficient for the general population. Patients with levels between 30 and 50 nmol/L are termed insufficient. The United Kingdom's Institute of Medicine supports the same recommendations; however, these values are not standardized and, as such, many use 30 nmol/L as the high end of osteomalacia, while levels up to between 75 and 120 nmol/L are at the high end of vitamin D insufficiency, associated with osteoporosis.[13]

Because no standard measurement exists, many laboratories will report values using different units. The next most common unit used is ng/mL, which is four tenths of the corresponding nmol/L measurement. Using the adjusted units, normal values would be closer to between 10 and 30 ng/mL for vitamin D deficiency and insufficiency.[14] For the purpose of standardization, values and units must be correctly used and appreciated. When assessing a patient's lab results, identify what that specific laboratory was testing and how they report their results.

Vitamin supplementation continues to be a controversial topic for physicians and scientists. On one hand, patients with low levels of certain vitamins certainly require supplementation. On the other hand, however, there is minimal evidence to support widespread supplementation for all individuals.[15-18] As it stands, the US National Institutes of Health recommends a daily intake of 600 IU vitamin D until the age of 70 years, when that value increases to 800 IU.[13] These intakes do not have to be obtained from supplements, but many diets lack the ability to obtain this much vitamin D[19]; the National Health and Nutrition Examination Survey (NHANES) study found that average individuals only obtain 144 to 288 IU per day without supplementation.[4]

Effect on Bone Fractures and Healing

Very few studies have been published on the efficacy of vitamin D supplementation on bone repair and healing. The vast majority of the research being done is on the effect of various bone healing modalities on at risk populations, mostly the elderly and the osteoporotic, and they are focused on prevention of fractures rather than healing. In this arena, large randomized control studies have been performed and meta-analyses of these reports have been run, as well. Through running a search of "fracture healing and vitamin D" in Google Scholar and PubMed and determining actual relevance to the topic, the list of articles in Table 1 was obtained. Most articles were either large prevention studies or animal model studies, with several unique studies found as well, ranging from 1945 until 2014.

Bischoff-Ferrari et al[5] notably found that vitamin D and calcium supplementation prevent nonvertebral fractures in a dose-dependent manner, with a more significant effect on the elderly. While not being a flaw in their research or conclusions, the conclusions they made were on fracture prevention, not specifically bone healing. Two landmark articles, which are widely cited examples of efficacy of bone healing without calcium, are animal model studies performed in the 1990s by Erben et al[37] and Delgado-Martinez et al.[36]

Erben et al[37] undertook a study to determine the effect of short-term, high-dose calcitriol on rat cancellous bone. These rats had no apparent fractures and no osteotomies were performed, however, the spines were observed for evidence of bone remodeling after administration of high-dose vitamin D over 3 consecutive days. Three separate experimental studies were performed, all with control groups, in order to determine calcitriol's role in calcium hemostasis, bone formation and parathyroid hormone levels, and finally on the number of osteoblastic precursor cells in the marrow. Among the results, rats treated with vitamin D were found to have pronounced hypercalcemia and hypercalciuria during treatment, increased osteoid production, increased osteoblast production, decreased osteoclast function, increased bone production rate, and no change in precursor stem cells. The authors state

Table 1.

Publications on Vitamin D and Fracture Healing.

Authors	Type	Year	Subject	Findings	Level of Evidence	Participants
Smith et al[20]	Prospective case series	2013	Prevention	Patients with a low-energy fracture of the foot or ankle were at particular risk for low vitamin D, especially if they smoked, were obese, or had other medical risk factors	3	75
Moran et al[11]	Prospective case series	2012	Prevention	The development of stress fractures in young recruits during combat training was associated with dietary vitamin D and calcium	3	74
Bischoff-Ferrari et al[4]	Meta-analysis	2012	Prevention	High-dose vitamin D supplementation was somewhat favorable in the prevention of hip fracture and any nonvertebral fracture in the elderly	1	31022
Bjelakovic et al[6]	Meta-analysis	2011	Prevention	Vitamin D_3 seems to decrease mortality in predominantly elderly women who are mainly in institutions and dependent care, though other forms of vitamin D are ineffective	1	94148
Bogunovic et al[21]	Retrospective case series	2010	Prevention	The prevalence of low serum levels of vitamin D among patients undergoing orthopaedic surgery is very common	3	723
Bischoff-Ferrari et al[5]	Meta-analysis	2009	Prevention	Nonvertebral fracture prevention with vitamin D is dose dependent, and a higher dose should reduce fractures by at least 20% for individuals aged 65 years or older	1	33265
Smith et al[22]	Randomized control trial	2007	Prevention	Annual injection of 300 000 IU vitamin D_2 is not effective in preventing non-vertebral fractures among elderly men and women	1	9440
Jackson et al[23]	Randomized control trial	2006	Prevention	Calcium with vitamin D supplementation resulted in a small but significant improvement in hip bone density, did not significantly reduce hip fracture, and increased the risk of kidney stones	1	36282
Melhus et al[24]	Prospective case series	1998	Prevention	High dietary intake of retinol (vitamin A) has a statistically significant association with osteoporosis	2	1295
Dawson-Hughes et al[25]	Randomized control trial	1997	Prevention	Dietary supplementation with calcium and vitamin D moderately reduced bone loss over three years compared to placebo	1	389
Parchi et al[26]	Case report	2014	Healing	Quicker fracture healing time with supplemental vitamin D	4	1

(continued)

Table 1. (continued)

Authors	Type	Year	Subject	Findings	Level of Evidence	Participants
Wolfl et al[27]	Prospective case series	2013	Healing	Findings could not confirm the increase of vitamin D_3 during the healing period but rather a slight decrease in humans	2	54
Hechtman et al[28]	Case report	2013	Healing	Refracture of a Jones fracture occurred in a vitamin D–deficient individual and has since healed with vitamin D supplementation	4	1
Kolb et al[29]	Prospective case series	2012	Healing	A balanced calcium homeostasis, obtained with calcium and vitamin D supplementation, is required for appropriate callus formation in postmenopausal women	2	94
Peichl et al[30]	Prospective case series	2011	Healing	Administration of parathyroid hormone 1-84 accelerates fracture healing in pelvic fractures and improves functional outcome over control group with only calcium and vitamin D supplementation	2	65
Iwamoto et al[31]	Randomized animal model	2010	Healing	Vitamin K_2 (menatetrenone) appears to be effective for promoting bone healing in a rat femoral osteotomy model	5	38
Holstein et al[32]	Randomized animal model	2010	Healing	Folate and vitamin B_{12} deficiency does not affect bone repair in mice	5	27
Fu et al[33]	Randomized animal model	2009	Healing	Vitamin D_3 could promote fracture healing by improving the histomorphology, mechanical strength, and tendency to increase lamellar bone in an ovariectomized rat model	5	40
Melhus et al[34]	Randomized animal model	2007	Healing	No decrease in mechanical strength, callus properties, or bone mineral density were noted in rats with vitamin D deficiency	5	72
Doetsch et al[35]	Randomized control trial	2004	Healing	Bone mineral density was improved in patients given vitamin D, as was fracture callus formation, though no correlation to fracture stability could be drawn	5	30
Delgado-Martinez et al[36]	Randomized animal model	1998	Healing	The administration of vitamin D_3 after experimental fracture significantly improved the strength of the fractured bone in elderly rats	5	15

(continued)

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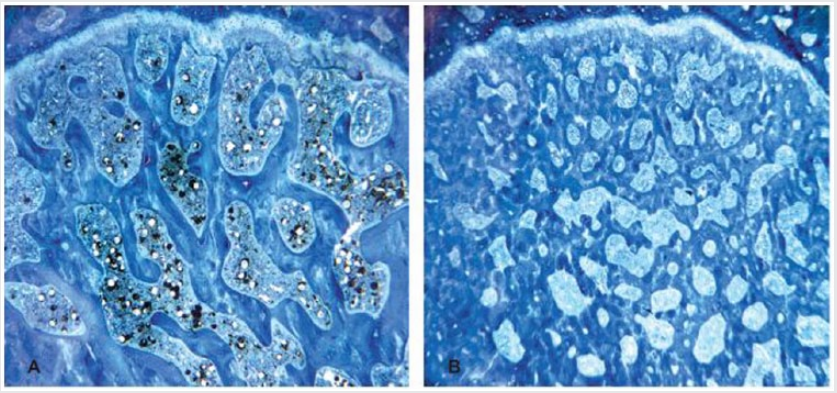
Authors	Type	Year	Subject	Findings	Level of Evidence	Participants
Erben et al[37]	Randomized animal model	1997	Healing	Short-term 1,25-$(OH)_2D_3$ treatment creates new bone remodeling units and augments osteoblast recruitment and osteoblast team performance in rat cancellous bone	5	92
Omeroğlu et al[38]	Randomized animal model	1997	Healing	With experimental fractures, the fracture load, the values of energy absorbed, and the flexural rigidity values of the vitamin D group were significantly higher than the control group; however, for intact bones, those values did not differ	5	20
Lidor et al[39]	Randomized animal model	1990	Healing	In normally fed chicks, local injection of inactive 24,25$(OH)_2D_3$ vitamin D_3 produced a stronger callus, while active 1,25$(OH)_2D_3$ vitamin D weakened the callus	5	72
Lidor et al[40]	Randomized animal model	1987	Healing	24,25$(OH)_2D_3$ at the higher doses has a direct local effect on cartilage and bone, while 1,25$(OH)_2D_3$ has no such effect in rachitic chicks	5	6
Dekel et al[41]	Randomized animal model	1983	Healing	24,25$(OH)_2D_3$ is essential for bone formation in addition to the known active vitamin D metabolite 1,25$(OH)_2D_3$	5	4 groups
Brumbaugh et al[42]	Randomized animal model	1982	Healing	Vitamin D_3 supplementation promotes bone repair in vitamin D–depleted chickens	5	34
Lindgren et al[43]	Randomized animal model	1981	Healing	Vitamin D_3 exaggerates bone resorption in rabbits with disuse or prednisolone related osteoporosis, impairing fracture healing	5	16
Copp et al[44]	Randomized animal model	1945	Healing	Vitamin A supplementation provided the most strength to callus repair in fractures of rat fibulas. Vitamin D supplementation lead to calcification of the callus, but without improved strength	5	210

Figure 1.

Despite the decreased trabeculation due to osteoporosis, as seen in (A), fracture healing progressed with no difference in experimentally treated rats. From Melhus et al.[34]



the likely mechanism of action was due to downregulation of parathyroid hormone, which was seen in their second experiment. Vitamin D was also found to suppress bone resorption by decreasing parathyroid hormone and by enhancing bone formation due to improved osteoblastic "team performance."[37] There is no mention of scaling up this procedure to human trials; however, the rat model they used is not a novel approach. The murine physiology tends to closely resemble ours for most processes, but further studies would need to be performed to duplicate these results before human conclusions can be drawn.

Delgado-Martinez et al[36] performed a randomized control study, 1 year later, simulating femoral fractures in rats and observing the healing process. One group of rats received vitamin D supplementation while the control group did not. Five weeks after the femoral shaft osteotomy, the femurs were extracted and put under torsional stress, to determine the strength of the resultant bone callus. Blood levels of vitamin D were obtained and those with higher levels had higher torsional strength. They reported that the vitamin D rat femurs had a "greater maximum shear force before failure."[36] This may or may not be applicable to humans or, more specifically, to the lower extremity, as it has yet to be duplicated. Many pedal fractures tend to be from a crushing, rather than shear, force which was not addressed by this study. The small sample of 15 rats may also call this study into question; however, the authors state that their results indicate vitamin D can improve the mechanical strength of bone in elderly rats, which may correlate to the elderly human population.

Clinically healthy rabbits have also been used to demonstrate the efficacy of vitamin D supplementation on fracture healing by Omeroğlu et al.[45] Again, using a single high dose of vitamin D_3, it was demonstrated that strength across the fracture site was increased with supplementation. There was in increase in strength required for refracture of the healed bone as well as increased rigidity measurements of both the developed fracture callus and the resultant bone. The authors also found that no vitamin D supplementation had no effect on healthy, nonfractured bone; this is an important finding from the article. The prior articles do not address the effect of vitamin D on nonfractured bones, while this one is clear that they found no increase in strength or significant remodeling between treatment and control groups. In another study, a single, intramuscular dose of 50 000 IU/kg was administered to healthy guinea pigs with manually fractured tibias. After 1 week, vitamin D led to increased organization and denser fibers in the resultant callus along with the observation of larger artery and veins. After 2 weeks, the experimental group already had development of an early cartilaginous callus along with some osteoprogenitor cells. Week 3 produced calcification of the callus in the experimental group, while by the fourth week the fracture site was "almost totally filled with new bone." The control group lagged behind by at least a week throughout the observations. As such, they determined that vitamin D had 4 separate mechanisms to improve bone healing: advancing the blood supply, improving osteoprogenitor cell response, increasing the amount of collagen in the callus, and increasing the efficacy of collagen organization. Another study suggests that, in spite of decreased trabeculation in femoral fracture healing without vitamin D, as seen in Figure 1, there was no decrease in fracture repair, bone mineral density at the fracture site, or biomechanical strength.[34]

Reports of vitamin D efficacy in the treatment of fractures for humans are rare. Moran et al[11] reported on an increase of stress fractures among elite military recruits who were deficient in vitamin D and calcium. They attribute the stress fractures to an increase in osteoclastic activity during bone remodeling within a background of already decreased vitamin D.[11] This study tends to be more reflective of the recent literature; that is to say most articles point toward both vitamin D and calcium playing a role together, rather than focusing on the importance of vitamin D as a sole entity. A randomized, double blind, placebo-controlled trial testing the efficacy of annual high-dose vitamin D injections failed to show any decrease in fracture risk with treatment in the general population. The group of nearly 10 000 participants had similar numbers of hip, wrist, and vertebral fractures between the control and treatment groups, while also failing to show a significant difference in preventing patient falls.[22] Similarly, a meta-analysis

consisting of more than 31 000 patients showed a nonsignificant 10% decrease in participants who received vitamin D, even with high levels of daily supplementation at 800 IU per day.[4]

It is without question that vitamin D is an integral mineral for calcium homeostasis. Current literature is indeterminate, however, as to the efficacy of supplementation for fracture healing in humans. Without being able to draw conclusions within the species, in general, it is tough to specifically make recommendations for lower extremity fractures. Vitamin D appears to be most efficacious in certain scenarios. Patients who can be described as elderly, osteoporotic, Caucasian, or female will receive more benefit from vitamin D_3 supplementation. The improvement will increase in a dose-dependent manner and will also, likely, improve with calcium supplementation as well.

Recently, 2 unique case reports offer support for vitamin D specifically for bone healing. A Jones fracture, which was fixated with an intramedullary screw, went on to adequate radiographic healing but suffered a refracture at 4 months postoperatively. The refracture healed after an additional 6 weeks, followed by a second refracture at 9 months after the initial injury. The vitamin D level was then assessed, and seen to be deficient at 20.6 ng/mL. After 8 weeks of high-dose vitamin D supplementation, the patient's vitamin D status rose to 39.0 ng/mL. Since then, he has been problem free for a year and a half.[28] Similarly, a single case report of a child who sustained a distal radius fracture followed by a refracture has been published. He was then diagnosed with hypovitaminosis D, with a vitamin D level of 22.2 ng/mL. Apart from vitamin D supplementation, both the initial fracture and the refracture were treated with long arm casting and immobilization. The second fracture, however, had significantly more callus formation after cast removal at 35 days.[26] It would seem as though the only difference between the first and second fractures was, in fact, the circulating vitamin D level. While only being single case reports, these 2 are unique in that they both eliminate many other variables.

Still, some research supports supplementation of other forms of vitamin D. The less active 24,25-dihydroxyvitamin D_3 has been shown to produce similar, or perhaps improved, healing efficacy versus what 1,25-dihydroxyvitamin D_3, notably when administered locally at the fracture site[39,40] and, while somewhat out of the scope of this article, other supplements and modalities have been hypothesized and tested with animal models, with varying degrees of success. Iwamoto et al[31] performed a study on femoral fractures in rats utilizing vitamin K_2 supplementation. They were able to show not only that vitamin K_2 was effective in limiting osteoclast inducer RANK-L, but that it also stimulated lamellar bone formation.[31] Parathyroid hormone has been given with success in healing pelvic fractures in humans, with or without calcium and vitamin D supplementation. And finally, Holstein et al[41] have shown that folate and B12 do not affect fracture healing.

Potential Study Design

The gold standard of medical research is the level 1 randomized control trial. Most research in podiatric medical journals are reported as levels 3 and 4, with more level 4 publications than levels 1 through 3 combined.[46] This topic deserves a higher level of evidence than is currently available. Using the following suggestions, any sufficiently trauma-oriented podiatric surgical residency should be able to obtain useable and duplicable results, establishing vitamin D efficacy in fracture healing.

The podiatric physician on call in the emergency department should have a protocol established that randomly assigns those patients presenting with foot and ankle fractures to 1 of up to 3 groups. These patients should be separated into, at minimum, a vitamin D supplementation group, a vitamin D and calcium supplementation group, and a placebo-control group, receiving inert pills or tablets. Ideally, further division of groups would occur, based on anything from location or mechanism of the fracture to primary treatments rendered, whether immediate or delayed open reduction/internal fixation or simply cast immobilization. For example, a small randomized group of nondisplaced metatarsal fractures would allow the researcher to eliminate internal fixation as a variable; all fractures could be treated nonoperatively with the patients being split into the thirds that were previously discussed.

For the sake of the research, a sufficiently high dose of vitamin D should be given while also minimizing the potential for detrimental effects. Because not all patients will be at the same starting level of vitamin D, the dose needs to be high enough to potentiate an effect but low enough to minimize risks. To prevent an additional variable, the dose should be standardized for everyone in the experimental group. Likely, 800 mg per day would be an acceptable amount. This dose is easily obtainable and managed, usually with just a single tablet. The vitamin D or the placebo could be assigned randomly through the use of sealed envelopes; the emergency department physician would be responsible for opening the envelope and distributing either a placebo or the vitamin D tablets.

All patients enrolled in the study should have vitamin D levels drawn immediately, in the emergency department, along with the standard complete blood count and comprehensive metabolic panel, to establish a baseline that can be compared to, likely at regular intervals of, potentially, 4, 8, and 12 weeks of follow-up. Plain film radiographs would also be obtained at the same regular intervals, to look for signs of bone healing, such as bony callus or trabeculation across the fracture site.

Conclusion

While several large studies exist regarding the efficacy of vitamin D and calcium supplementation for prevention of conditions, ranging from stress

fractures, to falls, and even mortality, very few studies on the efficacy of fracture healing and vitamin D supplementation have been written. Of the few studies specifically on vitamin D and fracture healing, even fewer are scaled to humans at this time. It is obviously difficult to obtain large, randomized control studies of traumatic medical conditions like fractures; however, it seems like literature is especially lacking here. High-trauma institutions could randomize patients into high-dose vitamin D versus placebo groups to help definitively demonstrate whether or not supplementation in the general population is effective. As it stands now, no conclusions can be drawn, so no treatment plans can be recommended for fractures in general, let alone specifically foot or ankle fractures. Basic animal models have shown that vitamin D, mostly in combination with calcium, may help fortify and accelerate bone callus formation, though these studies have yet to be scaled up to humans at this time. The best evidence we currently have tends to come from small case reports and series, which do offer some hope that vitamin D alone may help increase fracture healing, through stronger callus formation and by decreasing healing time. FAS

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