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# A Review of Vitamin D in Spinal Surgery: Deficiency Screening, Treatment, and Outcomes

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## ABSTRACT

In this review, we discuss the demonstrated value of vitamin D in bone maintenance, fracture resistance, spinal health, and spine surgery outcomes. Despite this, the effect of vitamin D levels in spine surgery has not been well described. Through this review of literature, several conclusions were drawn. First, despite the fact that a high number of spine surgery patients are vitamin D deficient, screening is not commonly performed. Second, vitamin D levels will not be achieved in a majority of these patients without supplementation. Last, inadequate vitamin D levels may increase the risk of pseudarthrosis. Given these findings, we suggest that many patients undergoing spinal surgery could be treated with vitamin D supplementation prior to surgery without the need for confirmatory testing for vitamin D deficiency. This is a more cost-effective method than screening all patients. However, future randomized trials and cost-effectiveness analyses are needed to determine the ultimate effects of vitamin D supplementation on clinical morbidity and surgical outcomes.

Other & Special Categories

Keywords: vitamin D, spinal surgery, outcomes, 25-hydroxyvitamin D, fusion

## INTRODUCTION

There is growing evidence that suggests vitamin D is a more critical component of maintaining overall health than previously understood. In composing this review, we found that supplementation of vitamin D has demonstrated to be protective against chronic diseases such as cancer, diabetes, osteoarthritis, and cardiovascular disease,<sup>1–3</sup> improve immunological function,<sup>2</sup> decrease all-cause mortality,<sup>4,5</sup> and improve muscle function and balance.<sup>6–10</sup> Of particular importance to spine surgeons, vitamin D is an integral part in the regulation of calcium homeostasis and bone health. As prior studies have demonstrated, low bone mineral density is a significant risk factor for vertebral fracture, instrumentation failure, and pseudarthrosis, signifying the fundamental role bone health plays in the fusion process.<sup>11–21</sup> Until recently, although hypovitaminosis D (the accepted term for insufficient or deficient levels of vitamin D) was significantly associated with low bone mineral density,<sup>22–24</sup> the effect of vitamin D levels on outcomes following spinal fusion were not well studied. Within the past several years, literature has

indicated that patients' bone and disc health as well as spinal fusion outcomes all may benefit from correcting their vitamin D levels.<sup>25</sup>

## Physiology

Vitamin D is acquired through dietary sources and supplements, as well as exposure to sunlight. The initial form created or ingested in the body is vitamin D<sub>3</sub>, which must be hydroxylated in the liver to 25-hydroxyvitamin D, or 25(OH)D, the major circulating form of vitamin D.<sup>26</sup> Analysis of 25(OH)D levels in the blood is the universally accepted method to determine overall vitamin D status.<sup>7,27–29</sup> Inactive 25(OH)D is converted to the active form 1,25-dihydroxyvitamin D primarily in the kidney, though other organs contribute minimally. Conversion to 1,25-dihydroxyvitamin D is a complex process regulated by parathyroid hormone (PTH), calcium, and phosphate levels, the details of which are not salient to the purpose of this article. In addition to regulating calcium and phosphorus absorption in the intestines, 1,25-dihydroxyvitamin D is crucial in bone turnover and fracture healing

through stimulating osteoblasts to synthesize new bone matrix proteins.<sup>30</sup>

### Screening

A survey study by Dipaola et al<sup>31</sup> reported on spine surgeon attitudes toward osteoporosis and osteomalacia screening. The authors reported that only 12% of surgeons obtain a metabolic bone laboratory panel before performing an instrumented fusion on a patient with suspected osteoporosis. In addition, only 20% of surgeons requested blood testing during the work-up of pseudarthrosis. In contrast, 44% of surgeons will obtain a dual-energy x-ray absorptiometry (DEXA) scan when suspecting osteoporosis prior to instrumented fusion, whereas 19% of surgeons will obtain a DEXA scan when assessing pseudarthrosis. When questioned regarding their rationale for not screening, 33% of all surgeons reported the information obtained would not affect their management, and 24% reported the lab results would not change the patient's degree of osteoporosis. It is interesting that neurosurgeons were significantly more likely than orthopedic surgeons to obtain these laboratory tests during their work-up (32% versus 15%).

There is significant debate regarding the appropriate screening protocol for vitamin D deficiency. Whereas some believe that vitamin D deficiency screening should be performed on all orthopedic patients,<sup>32,33</sup> others have advocated an algorithmic approach to screen only those at risk.<sup>34–36</sup> Women are at greater risk for vitamin D deficiency than men; other commonly considered risk factors are obesity, diabetes mellitus, older age, and reduced sunlight exposure.<sup>37–40</sup> However, not all research suggests that each of these contribute significantly. Thus, defining parameters for which patients to screen is difficult and may result in vitamin D-deficient patients not receiving treatment. Thomas et al<sup>29</sup> reported that at best, only 68% of patients who are vitamin D deficient would be identified using risk factors alone, and the only accurate method is to acquire blood 25(OH)D levels.

The cost associated with preoperative blood testing may be a deterrent to screening all patients. The 2010 Ontario Health Technology Assessment<sup>41</sup> reported an average cost of \$51.70 per 25-hydroxyvitamin D level and \$77.60 per 1,25-dihydroxyvitamin D level obtained. These costs resulted in a reported \$21.0 million spent on vitamin D screening in 2008, which increased to \$38.8 million in 2009. In

the United States, the cost of obtaining 25(OH)D levels has been reported at \$52.53 per test.<sup>42</sup> Although this is a relatively minor expense compared with the overall cost of surgery, the additional fee associated with screening may be unnecessary in a majority of patients. Furthermore, preoperative screening is inefficient due to the lack of a consistent cutoff for determining acceptable levels. Whereas most agree that 25(OH)D levels below 20 ng/mL are deficient, the level for “insufficient” is debated, ranging between 20 and 30 ng/mL. More recently, blood levels above 30 ng/mL have often been used as the “acceptable” range in published literature.<sup>30</sup>

### BACKGROUND AND CLINICAL STUDY

In other orthopedic fields, low vitamin D has been associated with a significant risk for fracture, impaired healing, and worse outcomes. A 2016 meta-analysis reported that 70% of all fracture patients have hypovitaminosis D, with a mean blood level of 19.5 ng/mL.<sup>24</sup> In addition, reports have indicated that as high as 66% of nongeriatric fracture patients may have vitamin D levels too low to maintain bone health and that have been associated with delayed fusion and higher rates of nonunion.<sup>20,21,43–46</sup> One study concluded that 57% of patients who experienced nonunion after total hip arthroplasty had hypovitaminosis D.<sup>14</sup> In contrast, a study assessing vitamin D levels in patients undergoing total hip arthroplasty reported similar functional outcomes between patients with low and patients with normal vitamin D levels.<sup>47</sup>

Although being relatively well studied in fracture literature, evidence regarding vitamin D levels and supplementation in spine surgery is rather limited.<sup>30</sup> Several studies have assessed vitamin D supplementation on patients with low back pain.<sup>43,44,46</sup> When assessing the effect of vitamin D on patients with chronic low back pain, one study reported that 95% of all patients (n = 341) and 100% of patients who were vitamin D deficient (n = 299) described significant improvement of their pain following supplementation.<sup>48</sup> Similarly, suboptimal concentrations of vitamin D have been associated with higher risk of cervical disc herniation.<sup>49</sup>

Despite the high prevalence of vitamin D deficiency, screening is not commonplace in spinal health care. Many patients with musculoskeletal disease have disc degeneration.<sup>50</sup> Several studies have observed that hypovitaminosis D<sup>36,43,51</sup> is correlated with increased lower back pain and that

pain relief can be accompanied by vitamin D supplementation.<sup>52,53</sup> Furthermore, the active form of vitamin D (1,25-dihydroxyvitamin D) has demonstrated an influence in types I and II collagen.<sup>54</sup> This same form has also been observed to affect the rate of cellular metabolism within the nucleus. Although some contend that the connection between degenerative spinal diseases and poor outcomes results from vitamin D deficiency, several more recent studies found no association.<sup>55,56</sup> Also potentially relevant in the care of possible spine surgery patients, vitamin D appears to affect bone-fracture healing. Lower vitamin D levels have been observed to correlate with lower bone densities, delayed rate of fracture healing, and screw loosening among patients who have undergone spine surgery.<sup>57</sup>

More recently investigators have focused on the association that deficient levels of vitamin D may have with patient outcomes following spine surgeries (Table). Several poor outcomes that have been hypothesized include decreased postoperative quality of life, elevated pseudarthrosis risk, and decreased functional neurologic performance.<sup>25,58</sup> The first spine-surgery-focused prospective study we were able to locate observed not only that vitamin D deficiency was common among patients undergoing surgery for spinal stenosis, but also that postsurgical vitamin D levels correlated with postoperative outcomes such as the Oswestry Disability Index and the EuroQol instrument, a five-dimensional three-level generic measure scores.<sup>36</sup> In a more recent prospective observational study among 31 cervico-thoraco-lumbar fusion patients, Ravindra et al<sup>58</sup> observed that patients with a low level of vitamin D had a higher (odds ratio = 3.449,  $P = .045$ ) nonunion rate, and longer median time duration to postoperative fusion (12 months vs 6 months,  $P < .001$ ) was associated with vitamin D levels. Whereas Ravindra et al<sup>58</sup> demonstrated that vitamin D deficiency approached higher rates of nonunion (assessed by radiographs) 12 months after spinal fusion (20% vs 38%,  $P = .063$ ), the authors acknowledged that their study may have been underpowered to detect statistical significance.

Other retrospective and case series studies over the past 3 decades have also investigated vitamin D levels in the setting of spine surgery.<sup>43,51,55,61</sup> Whereas Schofferman et al<sup>61</sup> and Donnally et al<sup>55</sup> observed no statistically significant association between vitamin D levels and pseudarthrosis, other

studies have indicated that increased vitamin D levels correlated with improved outcomes.<sup>43,51</sup> Waikakul et al<sup>43</sup> studied lumbar fusion patients who had been given 600 IU/d of vitamin D for 10 days (or until their levels normalized). The authors observed improved Japanese Orthopaedic Association (7.6 vs 4.2;  $P < .050$ ) and visual analog scale scores (7.7 vs 1.1;  $P < .001$ ) that correlated with vitamin D supplementation.<sup>43</sup> Similarly, in a study of transforaminal lumbar interbody fusion, Xu et al<sup>51</sup> observed significantly higher rates of lumbar fusion (95.24% vs 65.22%;  $P = .020$ ) among patients who received vitamin D supplementation.

A very common degenerative spinal disease among the elderly, spinal stenosis is associated with nerve impingement that can have etiologies such as ligament hypertrophy and degenerative spurs.<sup>35</sup> Vitamin D deficiencies are hypothesized to be associated with numerous other poor health statuses among patients who have lumbar spinal stenosis,<sup>36</sup> including an increased susceptibility to diabetes and cardiovascular comorbidities,<sup>62</sup> higher bone turnover,<sup>63</sup> and degraded locomotive ability.<sup>36</sup> In a 2013 study of 350 patients with lumbar spinal stenosis, Kim et al<sup>35</sup> reported that patients with severe back and leg pain were nearly 4 times more likely to suffer from vitamin D deficiency than patients with only mild to moderate pain. Furthermore, the researchers reported that lumbar stenosis was identified in 74.3% of the patient population in their lumbar stenosis study. They also reported that only 10 of the 350 patients within their study population had normal levels of vitamin D.

## TREATMENT CONSIDERATIONS

Supplementation with vitamin D has been shown to significantly improve blood levels of 25(OH)D.<sup>24,62</sup> When hypovitaminosis D is diagnosed, current treatment guidelines suggest a loading regimen of 50 000 IU vitamin D weekly, or 6000 IU daily, for 2 months. Following this loading phase, maintenance therapy of 1500 to 2000 IU/d should be continued.<sup>28</sup> Deficiencies can typically be corrected in 6 to 12 weeks, leading to stabilization of bone turnover.<sup>31</sup> Given that the optimum blood level for vitamin D remains unclear, the recommended daily vitamin D necessary to achieve adequate supplementation is also disputed. The Institute of Medicine<sup>65</sup> recommends 600 IU of vitamin D per day for those less than 70 years old and 800 IU for those over 70 years old. However,

**Table.** Study summary of vitamin D association with spine outcomes.

Author	Study Design	No. of Patients With Abnormal Vitamin D Concentration	Female/ Male, n	Mean Age, y	Vitamin D Form <sup>a</sup>	Spinal Region	Procedure Type	Results
Donnelly et al, 2019 <sup>55</sup>	Retrospective study	Preoperative: 36 Postoperative: 11	15/21 4/7	59.8 53.6	25(OH)D	Lumbar or thoracic	Fusion	Preoperative and postoperative vitamin D levels were not associated with risk of pseudarthrosis, revision, hardware failure, or pain scores
Ravindra et al, 2015 <sup>58</sup>	Prospective observational	31	75/58	57	25(OH)D	Cervico-thoraco-lumbar	Fusion	Vitamin D concentration was associated with nonunion rate and time to fusion
Xu et al, 2014 <sup>51</sup>	Retrospective	44	Not reported	Not reported	1,25(OH) <sub>2</sub> D	Lumbar	Transforaminal lumbar interbody fusion	Fusion rates and ODI scores were more favorable in the group that received vitamin D supplementation
Kim et al, 2013 <sup>35</sup>	Cross-sectional study	260	268/82	66.1	25(OH)D	Lumbar	N/A (spinal stenosis)	Vitamin D deficiency is highly prevalent in lumbar spinal stenosis patients and is associated with severe pain
Stoker et al, 2013 <sup>59</sup>	Cross-sectional study	Not reported <sup>b</sup>	176/137	55.2	25(OH)D	Cervical, thoracic, and lumbar	Fusion and/or revision surgery	There is substantially high prevalence of hypovitaminosis D in patients undergoing spinal fusion
Stoker et al, 2013 <sup>49</sup>	Retrospective study	27	37/54	52.1	25(OH)D	Cervical and thoracic	Fusion, disk replacement, and decompression	Vitamin D deficiency is associated with cervical disk herniation
Kim et al, 2012 <sup>36</sup>	Prospective cohort	31	31(F) <sup>c</sup>	67.7 deficient; 64.0 insufficient	25(OH)D	Lumbar	Decompression and posterolateral fusion	Postoperative ODI scores and EQ-5D index scores were significantly correlated with postoperative 25(OH)D level
Waikukul et al, 2012 <sup>43</sup>	Case series	9	6/3	39.2	25(OH)D	Lumbar	Fusion	Pain mean scores and JOA scores significantly improved in the group that received vitamin D supplementation
Zafeiris et al, 2012 <sup>60</sup>	Prospective longitudinal study	Not reported <sup>d</sup>	40(F)	70.6	25(OH)D	Thoracic and Lumbar	Kyphoplasty	Patients with recurrent fractures have lower vitamin D levels than patients without recurrent fractures after kyphoplasty
Pneumatikos et al, 2011 <sup>45</sup>	Case series	1	1	76	25(OH)D	Lumbar	Kyphoplasty	After kyphoplasty, vitamin D supplementation can improve muscle strength and decrease back pain
Schwalfenberg, 2009 <sup>44</sup>	Case series	6	3/3	51.8	25(OH)D	Lumbar	N/A (low back pain or failed back surgery)	Repletion of inadequate vitamin D levels shows significant improvement or complete resolution of chronic low back pain symptoms
Schofferman et al, 1990 <sup>61</sup>	Retrospective	7	21/26	41	1,25 (OH) <sub>2</sub> D	Lumbar	Fusion	There was no association demonstrated between pseudarthrosis and metabolic bone abnormalities

Abbreviation: JOA, Japanese Orthopaedic Association; NA, not applicable; ODI, Oswestry Disability Index.

<sup>a</sup>25(OH)D is calcidiol (also known as calcidiol, 25-hydroxycholecalciferol, or 25-hydroxyvitamin D), a prehormone that is produced in the liver; 1,25 (OH)<sub>2</sub>D is calcitriol (or 1,25-dihydroxycholecalciferol), the active form of vitamin D, normally made in the kidney.

<sup>b</sup>Of 313 adults undergoing surgical fusion at one institution, 57% and 27% were inadequate and deficient, respectively, in vitamin D.

<sup>c</sup>(F) indicates that patient subjects included only females and no males.

<sup>d</sup>No new-fracture group (n = 31) had higher levels of 25(OH)D than the adjacent-fracture group (n = 9).



several studies have suggested the recommended dietary allowance is not adequate to achieve satisfactory 25(OH)D blood levels, and consuming 700 to 2000 IU may be necessary to maintain blood levels greater than 30 ng/mL.<sup>7,28,29,66-73</sup>

This uncertainty in treatment dosing is highlighted in a study surveying orthopedic surgeons on the treatment of hypovitaminosis D. The authors<sup>74</sup> reported that greater than 45 different vitamin D dosing regimens were prescribed to fracture patients, depending on the population. In addition, the authors concluded that many orthopedic surgeons believe that fracture healing may be improved by vitamin D supplementation but frequently do not prescribe such treatment to their patients.

Although vitamin D supplementation is not commonplace, a higher number of orthopedic surgeons prescribe vitamin D than test for insufficiency.<sup>74</sup> With all other factors being equal, vitamin D supplementation is significantly less expensive than ordering 25(OH)D values, with reported costs between \$0.21 to \$1.46 per week.<sup>58</sup> Given the extremely high rate of vitamin D deficiency previously reported, it may be more cost effective, if time permits, to treat the deficiency rather than to test and then treat.

Whereas the morbidity associated with vitamin D supplementation appears relatively low, the decision to offer this treatment will likely need to be made between the patient and surgeon on a case-by-case basis. Although rare, there are risks of vitamin D toxicity with oversupplementation. The Institute of Medicine<sup>65</sup> reports that 25(OH)D blood levels of 50 to 60 ng/mL may put the patient at risk and should be avoided; similarly, they recommend a daily intake no higher than 4000 IU to avoid toxicity. The most common symptoms of acute intoxication are nausea, vomiting, constipation, and polyuria. Once recognized, there are many different treatment options available, depending on the severity and acuity of the toxicity.

Likewise, a flat recommendation to treat all patients with preoperative vitamin D, although seemingly inexpensive, can be complicated by numerous other implicit costs if the decision for surgery is not well planned. For example, the 6- to 8-week duration that is often required for loading patients with a weekly dose of vitamin D may have significant consequences with patient and clinical morbidity. Treating patients with extensive preoperative vitamin D therapy might be discouraged

among those who are enduring high levels of ongoing pain, disability, or other costly therapies. The clinical cost of delaying surgery can also have costly repercussions in terms of other pharmaceutical therapies required to control pain, lost patient wages, and a possible adverse effect of an extended duration of symptoms.

Unfortunately, few studies have assessed the effect of vitamin D supplementation or postoperative vitamin D levels on spinal fusion rates in humans. A study by Lawrence et al<sup>75</sup> examined the effect of daily parathyroid hormone (PTH) supplementation on rats undergoing spinal fusion. Though statistical significance was not reached, rats that received daily PTH demonstrated higher rates of fusion than rats who did not receive PTH.<sup>75</sup> Whereas PTH does not replicate vitamin D supplementation, their actions and biochemical functions are similar. Similarly, Metzger et al<sup>57</sup> assessed fusion rates in rats with varying levels of vitamin D; rats with increased vitamin D supplementation experienced higher fusion rates, bone volume, and bone density. It is interesting that one study demonstrated that vitamin D levels improve in the weeks to months following surgery even without supplementation, significantly so in those who were deficient preoperatively.<sup>36</sup> The authors hypothesized that the increased levels were likely a result of increased physical function achieved following surgery.

## CONCLUSIONS

This review of current literature regarding vitamin D levels and spine surgery has several salient points for spinal surgeons to consider. Despite a high number of vitamin D-deficient spine surgery patients, screening for hypovitaminosis D is not commonly performed. Second, adequate levels of vitamin D will not be achieved in a majority of patients with a deficiency without supplementation to their regular diet. Last, inadequate vitamin D levels may increase the risk of pseudarthrosis following spinal surgery.

Given the current literature, we advise against obtaining routine vitamin D levels in patients undergoing spinal surgery. Although it is true that a high number of patients undergoing spinal fusion will be vitamin D deficient, the utility of assessing the value before surgery is limited. By identifying patients with low vitamin D preoperatively, patients may be treated with supplementation and potentially minimize complications. However, testing

vitamin D levels is costly and often unwarranted in many patients. A potentially more appropriate approach would be to preemptively treat all patients with vitamin D and continue supplementation until arthrodesis has been confirmed. Although identifying which patients will actually benefit from supplementation has its merits, from a practical standpoint there is limited benefit.

With further cost analysis, we believe there is good reason to consider treating the majority patients given the relatively low up-front expense. The average cost of a revision surgery for pseudarthrosis is \$28 069. With vitamin D supplementation, it may be possible for a surgeon to effectively reduce pseudarthrosis rates and complication expenses at a fraction of the cost.<sup>76</sup> Whereas many spine surgeons may be underestimating the effect of vitamin D as a cost-effective method for improving spinal fusion,<sup>57</sup> a flat recommendation to treat all patients must also be weighed against other costs associated with patient and clinical morbidity. Likewise, although it does not appear to be cost-effective to screen all patients, if a patient who is prescribed vitamin D presents with pseudarthrosis, it may be beneficial to check 25(OH)D values to determine whether vitamin D may still be contributing or further work-up is required.

While these recommendations, high-quality research such as randomized trials and rigorous cost-effectiveness analysis are needed to make more definitive claims. Whereas the current literature may suggest vitamin D is likely associated with positive surgical outcomes, conclusive studies comparing the effects of vitamin D treatment are necessary to determine whether supplementation is beneficial, and if so, what dosing is optimal.<sup>58</sup>

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