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UPDATES IN SPINE SURGERY - TECHNIQUES, BIOLOGICS, AND NON-OPERATIVE MANAGEMENT (W HSU, SECTION EDITOR)

The Role of Preoperative Vitamin D in Spine Surgery

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Abstract

Purpose of Review Vitamin D is an essential micronutrient for human bone health and maintenance. Patients undergoing orthopaedic surgery with hypovitaminosis D may be at greater risk for worsened clinical outcomes. This narrative review aims to compile the current literature studying the effects of low preoperative vitamin D on spine surgery outcomes, creating a resource that clinicians can use to inform their practice.

Recent Findings Vitamin D deficiency predisposes to worse outcomes following spine surgery. Vitamin D supplementation may be beneficial in reducing the risk for adverse postoperative events; however, the literature is inconclusive regarding its efficacy in improving bone density and fracture risk.

Summary Spine clinicians should be aware of the increased risk for poor outcomes in patients with preoperative vitamin D deficiency. Future investigations are needed to better evaluate the benefits of preoperative vitamin D screening and supplementation on improving surgical outcomes in spine patients. These studies must also consider the effects on perioperative healthcare costs.

Keywords Vitamin D deficiency · Spine surgery · Bone mineral density · Outcomes

Introduction

Vitamin D is a fat-soluble micronutrient important for regulating calcium-phosphorus metabolism [1•]. Vitamin D deficiency, or hypovitaminosis D, typically leads to increased parathyroid hormone (PTH) secretion, leading to osteoporosis, increased fracture risk, and lower bone density [1•]. Vitamin D deficiency is common with an estimated prevalence of over 1 billion individuals worldwide [2]. Postmenopausal women may be at greater risk, particularly those with osteoporosis [3]. These comorbidities can predispose worsened outcomes in spine surgery, including pseudoarthrosis and instrumentation failure [1•].

The importance of vitamin D in musculoskeletal development and bone healing makes it particularly relevant in spine surgery patients, who may be at greater risk of deficiency [4, 5]. The effects of vitamin D deficiency on bone health are important for spine health, as low bone mineral density predisposes to poor outcomes (i.e., instrumentation failure, pseudarthrosis, vertebral fracture) [6–10]. Given the frequency of hypovitaminosis D in patients and its potential implication in surgical outcomes, it is crucial for spine clinicians to be aware of the current literature. The aim of this article is to comprehensively review the existing literature examining vitamin D deficiency and spine surgery outcomes, the potential benefits of preoperative supplementation, and financial considerations.

Prevalence and Risk Factors

In the general population, hypovitaminosis D has been cited at approximately 30% using a threshold serum 25(OH)D concentration of 20 ng/mL [11]. Several studies have evaluated the prevalence and risk factors for hypovitaminosis D in spine surgery patients summarized in Table 1. At a single center in Germany, Schmidt et al. reported a high prevalence of poor bone mineral density in 144 patients preoperatively [12].

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Table 1 Prevalence and risk factors of vitamin D deficiency

Author	Year	Sample description	Findings
Schmidt et al.	2018	*N*=144 73.6% had vitamin D levels < 30 ng/mL 36.8% had vitamin D levels < 20 ng/mL	High prevalence of vitamin D deficiency in preoperative spine surgery patients
Xu et al.	2019	*N*=360 53.6% had vitamin D levels < 20 ng/mL 46.4% vitamin > 30 ng/mL	Risk factors included higher BMI, female sex, smoking, lack of supplementation, moderate or severe pain by VAS
Stoker et al.	2013	*N*=313 57% < 30 ng/mL 27% < 20 ng/mL	Risk factors included younger age, lack of supplementation history, BMI, increase in ODI and/or NDI
Donnally et al.	2019	*N*=97 37.1% vitamin D levels < 30 ng/mL 48.5% vitamin D levels = 30-50 ng/mL 29.8% > 50 ng/mL	Risk factors included younger age and higher BMI

25(OH)D and PTH levels were measured in the patients, with vitamin D inadequacy defined as < 30 ng/mL and deficiency as < 20 ng/mL. A total of 73.6% of patients were vitamin D inadequate, while 36.8% were deficient. Notably, 34.7% of patients showed secondary hyperparathyroidism. Given that increased PTH secretion leads to increased bone resorption and reduced bone density, it is important to understand the resulting consequences. For instance, it has been reported that pedicle screw loosening is tied to low BMD [13]. Additionally, osteoporosis is known to result in longer operative times for spine patients, which is tied to overall complications [14]. A limitation of this study includes that the mean age of patients was 70 years, which may skew the prevalence of osteoporosis. There may also be a selection bias due to limited sun exposure in northern European countries compared to other regions of the world.

Xu et al. found that the overall prevalence of hypovitaminosis D in their study population of lumbar spine surgery patients was 46.4% [1•]. Similarly, Stoker et al. defined vitamin D inadequacy as < 30 ng/mL and deficiency as < 20 ng/mL [15]. In their study cohort comprised of spinal fusion patients, 57% of patients were categorized as vitamin D inadequate, while 27% were deficient. The study by Stoker et al. ($N = 313$) also specifically evaluated risk factors associated with hypovitaminosis D in patients undergoing spinal fusion at a single medical center [15]. There was no difference in vitamin D deficiency by sex, but there was a significant difference by age, with vitamin D–deficient patients younger than those without deficiency ($p < 0.01$). A multivariate analysis in this study found that a lack of supplementation history and increases in BMI or disability score were significant predictors of vitamin D deficiency. Notably, each one-point increase in disability index scores amongst subjects resulted in 3% lower odds of having adequate levels of 25(OH)D. Patients who received vitamin D supplementation in the past showed higher 25(OH)D levels compared to those without supplementation ($p < 0.01$). Importantly, those with previous vitamin D supplementation histories were older ($p < 0.01$). This illustrates a high prevalence of vitamin D deficiency in the population undergoing spine surgery and emphasizes the importance of evaluating the need for supplementation in younger patients.

In agreement, a study by Donnally et al. found that the age at time of surgery was indicative of vitamin D levels, with older patients having higher serum levels of vitamin D both preoperatively ($p = 0.03$) and postoperatively ($p = 0.01$) [16]. Patients taking preoperative vitamin D supplements were significantly older than those without supplementation ($p < 0.0001$). Furthermore, BMI had an inverse association with preoperative levels of vitamin D. Overall, current literature provides evidence that younger patients may be at risk of hypovitaminosis D due to lack of supplementation and that there is a high prevalence of hypovitaminosis D in the spine surgery population.

Outcomes

Effects of Vitamin D on Surgical Outcomes

Multiple studies have reported on clinical outcomes of spine surgery patients with hypovitaminosis D which are outlined in Table 2. A study by Xu et al. ($N = 360$) evaluated markers for vitamin D in patients undergoing either posterior lumbar interbody fusion or posterolateral fusion [1•]. The authors measured serum levels of 25-hydroxy vitamin (25(OH)D),

Table 2 Vitamin D deficiency outcomes

Author	Year	Sample description	Findings
Schmidt et al.	2018	*N*=144	Vitamin D inadequacy and deficiency are associated with poor bone mineral density
		73.6% had vitamin D levels < 30 ng/mL	
		36.8% had vitamin D levels < 20 ng/mL	
Xu et al.	2019	*N*=360	Vitamin D–deficient patients had worsened JOA and VAS at 3 months postoperatively
		53.6% had vitamin D levels < 20 ng/mL	
		46.4% vitamin > 30 ng/mL	
Ravindra et al.	2015	*N*=133	Time to spinal fusion significantly longer in vitamin D–deficient patients
		23% had vitamin D levels < 20 ng/mL	
Kim et al.	2012	*N*=31	Vitamin D–deficient patients had significantly worse ODI and EQ-5D scores
		35.5% vitamin D levels = 20-30 ng/mL	
		64.5% vitamin D levels < 20 ng/mL	
Donnally et al.	2019	*N*=97	Lower preoperative vitamin D levels significantly associated with fewer levels of vertebrae fused
		37.1% vitamin D levels < 30 ng/mL	
		48.5% vitamin D levels = 30–50 ng/mL	
		29.8% > 50 ng/mL	
Khalooeifard et al.	2022	*N*=1142	Significantly increased ODI in vitamin D–deficient group
		38.5% < 30 ng/mL	
Ko et al.	2020	*N*=61	ODI was significantly lower and MCS and PCS were significantly higher in vitamin D–supplemented group 12 and 24 months postoperatively
		44.3% received 100,000 vitamin injection	
Xu et al.	2014	*N*=44	Higher fusion rates and lower ODI in group with vitamin D supplementation
		47.7% received vitamin D3 supplementation	
Waikakul et al.	2012	*N*=9	VAS and JOA scores improved significantly at 6-month mark with vitamin D supplementation
		600 IU vitamin D supplementation for 10 days	
Skrobot et al.	2020	*N*=30	Vitamin D supplementation group had significant reductions in RF
		3200 IU vitamin D supplementation for 5 weeks before surgery	
Jackson et al.	2006	*N*=448	Increased hip bone density in treatment group at 3, 6, and 9 months
		50.6% received 1000 mg calcium and 400 IU vitamin D daily	
		49.4% received placebo	
LeBoff et al.	2020	*N*=771	No benefit in BMD at 2-year time point
		50.3% received vitamin D supplementation, 49.7% received placebo	
Bischoff-Ferrari et al.	2012	*N*=31,022	High intake of vitamin D leads to a reduction in the risk of fracture
		50% received vitamin D supplementation, 50% received placebo	

N-terminal midfragment of osteocalcin (N-MID), and β type 1 collagen carboxyl terminal peptide (β-CTX). Patients with 25(OH)D levels < 20 ng/mL were characterized as deficient ($N = 193$), with the remaining 167 individuals being non-deficient. Preoperatively, there were no differences in Japanese Orthopedic Association (JOA) and Oswestry Disability Index (ODI) between groups; however, the vitamin D–deficient group had higher visual analogue scale (VAS) scores (4.52 ± 1.66 vs 3.50 ± 1.39; $p < 0.001$). Postoperatively, vitamin D–deficient patients had worsened JOA (15.13 ± 2.29 vs 16.05 ± 2.61; $p < 0.001$), ODI (14.54 ± 1. 20 vs 13.80 ± 1.54; $p < 0.001$), and VAS (2.34 ± 0.45 vs 2.01 ± 0.56; $p = 0.027$) at 3

months. Independent predictors of vitamin D deficiency were body mass index (BMI), female sex, smoking, lack of supplementation, and moderate or severe pain by VAS. It should be noted the 3-month follow-up time in this study may not encapsulate the long-term effects of vitamin D deficiency postoperatively.

A prospective study by Ravindra et al. similarly evaluated vitamin D levels in patients undergoing elective spinal fusion (n = 133), measuring rates of nonunion and time to fusion [17]. Patients were characterized as deficient (< 20 ng/mL), insufficient (20–30 ng/mL), and sufficient (> 30 ng/mL). The fusion rate at 12 months was 84%. A logistic regression found that vitamin D deficiency was an independent driver for nonunion (OR: 3.449, 95% CI 1.029–11.561, p = 0.045). Kaplan-Meier survival analyses evaluated time to fusion, finding vitamin D–deficient patients took significantly longer than insufficient and sufficient patients (12 vs 8 vs 6 months, respectively, p = 0.001). This study is limited by a small sample and relatively short follow-up period; further larger and longitudinal studies evaluating fusion in vitamin D–deficient patients may conclusively quantify extended fusion times.

A prospective study by Kim et al. assessed the relationship between preoperative vitamin D levels, postoperative vitamin D status, and surgical outcomes [18•]. The study included 31 female patients who had posterior decompression and posterolateral fusion for lumbar spinal stenosis. Patients had 25(OH)D levels measured preoperatively and at 1-year postsurgery. Patients were grouped as deficient (< 20 ng/mL), insufficient (20–30 ng/mL), and sufficient (> 30 ng/mL) based on preoperative vitamin D levels. No patients were vitamin D sufficient; 11 patients were categorized as insufficient, and 20 patients were deficient. There were no differences in preoperative patient-reported outcomes (PROs), measured by ODI, EuroQol 5-dimension (EQ-5D) index, and EQ-5D visual analogue scales. In deficient patients, a significant increase was observed between preoperative and 1-year postoperative 25(OH)D levels (11.1 to 14.2 ng/mL; p = 0.017). There was no significant change within the insufficient group (p = 0.594). Postoperatively, a total of 18 patients were vitamin D deficient, 5 insufficient, and 5 sufficient. The deficient group post-surgery showed significantly worse outcomes regarding ODI (p = 0.029) and EQ-5D index scores (p = 0.021) than other groups. The researchers hypothesized that the surgical intervention improved physical capabilities in patients, leading to an increase in serum 25-OHD levels via increased mobility. As the authors explained, greater function would lower bone turnover, increase exposure to sunlight, and improve nutrition. A limitation of this study was that postoperative vitamin D intake was not measured rendering it a potential confounding variable. Although this study has limitations, there may be an improvement in vitamin D status after spine surgery, with postoperative vitamin D levels associated with better patient-reported outcomes.

Donnally et al. conducted a single-center study and found that lower preoperative vitamin D levels were significantly correlated with fewer levels of vertebrae fused in patients undergoing lumbar fusion [16]. Vitamin D levels did not have a significant correlation with VAS at 1 year, rates of postoperative hardware complication, pseudoarthrosis, or revision surgery (p > 0.05). A limitation of this study was that the measured levels of vitamin D were not taken uniformly amongst all the patients.

Additionally, a recent meta-analysis conducted by Khalooeifard et al. pooled 1188 patients undergoing elective spinal fusion surgery and analyzed the relationship between preoperative vitamin D deficiency with VAS and ODI [19]. No significant difference was found between vitamin D–deficient patients and those with normal levels when analyzing VAS. However, there was a significant increase in ODI when examining the vitamin D–deficient group compared to the group with normal levels (weighted mean difference: 4.82, 95% CI 0.84–8.80). Overall, the studies that have investigated the impact of vitamin D levels on spine surgery outcomes reveal two trends: lower fusion rates and worse patient-reported outcomes in patients with vitamin D deficiency.

Effects of Vitamin D Supplementation on Surgical Outcomes

Studies have also evaluated the effects of vitamin D supplementation on spine surgery outcomes with conflicting findings. Ko et al. conducted a retrospective analysis of patients with lumbar spinal stenosis (LSS) who were vitamin D deficient (< 20 ng/mL) [20]. A total of 61 patients were divided into a supplementation group (IM injection of 100,000IU vitamin D3) and a control group. The groups were evaluated for functional outcomes via a Korean version of the ODI and the Roland-Morris Disability Questionnaire (RMDQ). Preoperatively, there were no differences in ODI and RMDQ scores by group. At the 12-month (p = 0.034) and 24-month (p = 0.0002) mark, the authors found that ODI in the supplementing group was significantly lower. However, there was no significant difference in RMDQ at these time points. The Short Form Survey (SF-36) was used to assess quality of life in the patients spanning both mental and physical component scores (MCS and PCS). Preoperatively, there was no significant difference in these scores. At 12-months and 24-months, patients in the supplementation group reported significantly higher scores in the MCS (12 months: p = 0.005, 24 months: p < 0.005) and PCS (12 months: p = 0.001, 24 months: p < 0.005).

Xu et al. studied 44 patients with osteoporosis and lumbar degenerative disease undergoing transforaminal lumbar interbody fusion, dividing them into two groups: (1) those receiving supplementation and (2) controls given placebo [21]. They found higher fusion rates in the supplementation

group at the last follow-up time point, which was between 12 and 27 months (95.24% vs 65.22%, $p = 0.02$). The researchers reported a significantly lower ODI in the experimental group compared to placebo ($p < 0.05$).

Similarly, Waikakul et al. reported on 9 patients in a case series evaluating vitamin D deficiency in patients who had failed back surgery syndrome after lumbar fusion [22]. Patients were given 600 IU of daily vitamin D supplementation for 10 days or until normal vitamin D levels were reached. At 6 months, the VAS score had improved from 7.7 to 4.2 ($p < 0.05$) and the JOA score improved from 7.6 to 11.1 ($p < 0.001$). The study indicated that supplementing with vitamin D could help treat failed back surgery syndrome; however, more robust clinical data with larger sample sizes are required before conclusive recommendations.

Recently, a randomized controlled trial conducted by Skrobot et al. investigated the effect of vitamin D supplementation on postoperative rehabilitation in patients undergoing anterior cervical discectomy and fusion (ACDF) [23]. The study included a total of 30 patients who were randomly administered either placebo or vitamin D (3200 IU/day) for 5 weeks before surgery. Functional outcomes included risk of falls (RF), limits of stability, postural stability, and the Romberg test, measured at various time points: before supplementation, 5 weeks after supplementation, 4 weeks postoperatively, and 10 weeks after rehabilitation. The results showed that patients with supplementation saw significant reductions in RF after 5 weeks of supplementation, which continued to decrease after rehabilitation. Meanwhile, the placebo group had no change in RF. All other outcomes significantly improved for both groups, though changes in postural stability were more pronounced in the supplementation cohort. These findings suggest that vitamin D supplementation may provide benefits that even appear after undergoing spine surgery.

Effect of Vitamin D Supplementation on Bone Mineral Density

Increased bone mineral density may be a contributing factor to enhanced outcomes following vitamin D supplementation. A double-blind, randomized controlled trial conducted by Jackson et al. investigated the effect of vitamin D and calcium supplementation on the bone density of 36,283 postmenopausal women [24]. Subjects were randomly assigned to either receive 1000 mg calcium and 400 IU vitamin D daily or placebo. Intention-to-treat analysis revealed an increased hip bone density at 3, 6, and 9 months in the treatment group. Although insignificant, the treatment group also had increased spine and total bone density. Similarly, a randomized controlled trial conducted by LeBoff et al. found that supplemental vitamin D showed no significant benefit in BMD at the spine, femoral neck, hip, and whole body when compared to placebo at the 2-year time point [25]. Furthermore, a systematic review and meta-analysis found no significant effect of vitamin D on BMD in the spine; however, dosing vitamin D at levels less than 800 IU per day could have positive benefits on the lumbar spine (0.4% CI: 0.0 to 0.8) [26]. The overall findings from this meta-analysis show marginal benefit to vitamin D supplementation in improving bone density. Interestingly, other studies have reported that vitamin D supplementation can benefit fracture risk [27, 28]. Thus, there is a divide in the literature regarding vitamin D supplementation and its overall benefit.

Financial Considerations of Vitamin D Supplementation

Cost is a factor driving decision-making regarding preoperative vitamin D screening and supplementation. The 2010 Ontario Health Technology Assessment found that screenings of 25(OH)D and 1,25-dihydroxyvitamin D cost $51.70 and $77.60, respectively [29]. In the USA, the cost of 25(OH)D is about $52 per test. The cost of supplementation, however, is much lower, ranging from $0.21 to $1.46 weekly. Future research should weigh the cost-effectiveness and clinical utility of preoperative screenings versus just supplementation. There are few risks associated with vitamin D supplementation as toxicity can be minimized by limiting daily intake to below 4000 IU. Decision to delay surgery based on hypovitaminosis D needs to be done on an individual basis, based on a thorough evaluation of neurologic status and disability. It is important to note that the effect of vitamin D supplementation on improving bone density is still in question, with supplements yielding only marginal benefit [26]. Additionally, the physiological mechanism underlying undesirable surgical outcomes in vitamin D–deficient patients remains in question. Given this uncertainty, there is a lack of consensus when it comes to recommending vitamin D supplementation as a preventive measure, as well as limited evidence to delay surgery for preoperative vitamin D supplementation. Additional prospective research with long-term follow-up would help clearly elucidate a clinically pragmatic supplementation protocol.

Conclusions

Current investigations have illustrated a link between hypovitaminosis D and poor postoperative outcomes. However, these studies are limited by small sample sizes, short-term follow-up, and poor control of confounders. Supplementation may mitigate adverse postoperative outcomes; however, the literature remains mixed when it comes to BMD and fracture implications. The Endocrine Society guidelines for adults recommend at least 600 IU of daily

vitamin D and 800 IU daily for adults older than 70 [11]. Future analyses should attempt to account for confounders like postoperative vitamin D supplementation and sunlight exposure when looking at postoperative outcomes. There is a gap in the literature in studying preoperative vitamin D status and postoperative medical endpoints, and a rift in the literature regarding bone density and its relationship to vitamin D. Future research should elucidate the physiological underpinnings of complications observed in patients with hypovitaminosis D to help serve as the foundation for future clinical recommendations.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of interest Anitesh Bajaj, Rohan M. Shah, Alyssa M. Goodwin, Steven Kurapaty, Alpesh A. Patel, and Srikanth N. Divi declare that they have no conflict of interest.

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