Spine

SPINE Volume 40, Number 19, pp 1536-1541

EPIDEMIOLOGY

Vitamin D Levels and 1-Year Fusion Outcomes in Elective Spine Surgery

A Prospective Observational Study

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Study Design. Prospective observational study.

Objective. To investigate the association of perioperative vitamin D levels and nonunion rates and time to fusion in patients undergoing elective spine fusion.

Summary of Background Data. Although there is a clear link between bone mineral density and the risk of osteoporosis, it is unclear whether low vitamin D levels affect rates and timing of spinal fusion.

Methods. Serum 25-OH vitamin D levels were measured perioperatively in adults undergoing elective spinal fusion between 2011 and 2012. Vitamin D levels <20 ng/mL were considered deficient. Univariate and multivariate logistic regression were performed to identify independent predictors of pseudarthrosis/nonunion within a minimum follow-up period of 12 months. Kaplan-Meier analysis was used to compare time to fusion between groups.

Results. Of the 133 patients, 31 (23%) demonstrated vitamin D deficiency. Mean patient age was 57 ± 13 years; 44% were female and 94% were Caucasian. The cervical spine was fused in 49%, the lumbar spine in 47%, and the thoracic spine in 4%. Mean construct length was 2 levels (range 1–16). At 12-month follow-up, 112/133 (84%) patients demonstrated fusion (median time to fusion 8.4 mo). Nonunion at 12 months was associated with vitamin D deficiency (20% of patients with adequate vitamin D level *vs.* 38% of vitamin D-deficient patients, $P = 0.063$). Kaplan-Meier survival analysis demonstrated time to fusion was significantly longer in the vitamin D-deficient group (12 *vs.* 6 mo, $P = 0.001$). On multivariate analysis, vitamin D deficiency was an independent predictor of nonunion (odds ratio 3.449, $P = 0.045$) when adjusted for age, sex, obesity, fusion length, location, graft type, smoking, and bone morphogenetic protein use.

Conclusion. Vitamin D levels may affect nonunion rate and time to fusion. These results offer insight into the importance of the metabolic milieu for bony fusion as well as a potential avenue for therapeutic intervention.

Key words: vitamin D deficiency, pseudarthrosis, Kaplan-Meier survival analysis.

Level of Evidence: 3

Spine 2015;40:1536–1541

Spinal arthrodesis has become the mainstay of treatment for severe spinal deformity, spinal instability, spondylolisthesis, and symptomatic degenerative disease.[1] Its primary goal is to develop an osseous bridge between adjacent motion segments to prevent motion, relieve pain, and facilitate neurological recovery. Bony fusion is a dynamic process involving osteocytes, osteoclasts, and osteoblasts.[1] Level of calcium availability and vitamin D balance may affect the metabolic milieu available for development of a fusion mass. Low bone mineral density (BMD) remains the most common cause of spine fractures,[2] and lower BMD secondary to osteoporosis and osteomalacia represents a known significant risk factor for both bony fracture and spinal instrumentation failure.[3–7] Our group[8] and Stoker *et al*[9] independently demonstrated a high rate of vitamin D deficiency in patients undergoing spinal instrumentation. Although there is a clear link between BMD and the risk of osteoporosis, it is unclear whether low vitamin D levels can affect rates of fusion, time to fusion, or the incidence of instrumentation failure.

The present study was designed to evaluate the relationship between vitamin D status and bony fusion in patients undergoing elective spinal instrumentation. A secondary goal of the study was to evaluate the association between vitamin D levels and the time to fusion. We hypothesized that patients with vitamin D deficiency would be at higher risk of nonunion

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Acknowledgment date: April 21, 2015. Acceptance date: June 23, 2015.

The manuscript submitted does not contain information about medical device(s)/drug(s).

No funds were received in support of this work.

Relevant financial activities outside the submitted work: board membership, consultancy, grants, payment for lectures.

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DOI: 10.1097/BRS.0000000000001041

and would demonstrate increased time to fusion because of the adverse metabolic environment created by the deficiency.

MATERIALS AND METHODS

Patient Population

After the Institutional Review Board approved the study, we prospectively recruited patients undergoing elective spinal fusion at a single academic, tertiary referral institution between November 2011 and December 2012. Adults over the age of 18 years carrying a diagnosis of spinal spondylosis requiring spinal fusion were eligible to participate. Those who were monitored with a minimum of 12-month follow-up were included. To maintain uniformity of the population, patients admitted with traumatic spinal fracture, infection, or cancer-related instability requiring stabilization were excluded from study participation.

Data Collection

Patient demographic information, medical comorbidity information, medication use, and history of vitamin D supplementation were recorded. In addition, the use of steroids for chronic disease (*e.g.*, rheumatoid arthritis), use of vitamin D supplementation preoperatively (and preoperative vitamin D levels, if measured), and preoperative disability indices were recorded. Vitamin D levels were assessed in all patients during the perioperative period (within 72 hr postoperatively). A patient was deemed to be vitamin D deficient with a vitamin D level less than 20 ng/mL. A vitamin D level of 20 to 30 ng/mL was considered insufficient. Patients whose vitamin D levels were greater than 30 ng/mL had normal levels of vitamin D. Surgical details including the length and location (cervical, thoracic, or lumbar) of the fusion construct, the number of motion segments, the use of graft material (allograft, autograft, both) and bone morphogenic protein-2 (BMP-2), the instrumentation type, and revision status were noted. Imaging assessment of fusion was performed at 6 weeks, 3 months, 6 months, and 12 months. Postoperative disability index (Visual Analogue Scale (VAS), Neck Disability Index (NDI), Oswestry Disability Index (ODI)) scores were also recorded at the same time points.

Assessment of Fusion

Radiological fusion was defined as the presence of bone trabeculation, without evidence of instrumentation loosening or breakage, and no observed motion between the graft and instrumentation.[10,11] Fusion was measured both as time to event and categorically (fused/nonfused). Additional follow-up computed tomography (CT) imaging was used to assess fusion at the surgeon's discretion or in the event of inconclusive radiographs.

Statistical Analysis

Data were summarized using means and standard deviations for continuous variables and counts and frequencies for categorical variables. Univariate statistical analysis was performed to identify the unadjusted association of basic demographic and medical comorbidity covariates with the presence of vitamin D deficiency and nonunion. Multiple logistic regression analysis was performed to assess independent patient-level risk factors for nonunion. 2 separate Kaplan-Meier survival analyses were performed using the log-rank test: (1) to compare time to fusion between the vitamin-D-deficient (<20 ng/mL) group and the non-deficient group (>20 ng/mL) and (2) to compare time to fusion among the vitamin D-deficient (<20 ng/mL), vitamin D-insufficient (20–30 ng/mL), and normal vitamin D (>30 ng/mL) groups. Statistical significance was established using a cutoff of $P < 0.05$. Data were analyzed using SPSS version 20.0 software (IBM Corp., Armonk, NY).

RESULTS

Patient Characteristics

133 patients satisfied the inclusion criteria. Patient demographics and univariate analysis are reported in Table 1. The mean age of the patients was 58 ± 13 years; 44% were female and 94% were Caucasian. Of all patients, 49% underwent cervical fusion, 47% underwent lumbar fusion, and 4% underwent thoracic fusion. Mean construct length had 2 levels (range 1–16). The average body mass index (BMI) was 30 ± 6 for all patients; BMI did not influence rate of fusion or time to fusion in any group. Preoperative NDI score was 21 ± 9 for all cervical patients; postoperative NDI was 15 ± 11. Preoperative ODI score was 23 ± 9 for all patients; postoperative ODI for all patients was 16 ± 10. There was no significant difference between the fusion and nonunion groups for these scores. The mean serum 25-OH vitamin D level was 27.8 ± 12.8 in the perioperative period. Of the 133 patients included, 31 (23%) demonstrated vitamin D deficiency.

Fusion

Of 133 patients, 112 patients (84%) demonstrated fusion by 12 months on routine flexion/extension radiographical studies; 21 (16%) failed to demonstrate adequate bony fusion by 12 months (Table 1). On univariate analysis, there were no significant differences between age, race, comorbidities (smoking, diabetes), location of surgery, length of fusion, approach (anterior *vs.* posterior *vs.* combined), graft type, revision surgery, use of BMP, or NDI and ODI with respect to fusion status. There was an association between vitamin D deficiency and nonunion that approached, but did not reach, statistical significance on univariate analysis (38% *vs.* 19.6%, $P = 0.063$) (Table 1). On multivariate analysis, after controlling for age, sex, and fusion length, vitamin D deficiency was independently associated with nonunion (aOR 3.449 [1.029, 11.561]) (Table 2).

Time to Fusion

2 separate Kaplan-Meier survival analyses were performed for fusion in the 112 patients in whom fusion was achieved: (1) to compare time to fusion between the vitamin D-deficient (<20 ng/mL) group and the nondeficient group (>20 ng/mL) and (2) to compare time to fusion among the vitamin D-deficient (<20 ng/mL), vitamin D-insufficient (20–30 ng/mL), and

TABLE 1. Demographics of Patients Undergoing Spinal Fusion Procedures and Univariate Analysis Assessing Effect on Fusion Rates

Variable	All Patients (N = 133)	Patients With Fusion (N = 112)	Patients With Nonunion (N = 21)	*P*
Mean age in yr (±SD)	57.6 ± 12.7	57.0 ± 12.7	59.0 ± 12.6	0.586*
Age (no. of patients,%)				0.340†
<50 yr	33 (24.8)	29 (25.9)	4 (19.0)	
50–60 yr	36 (27.1)	28 (25.0)	8 (38.1)	
60–70 yr	36 (27.1)	33 (29.5)	3 (14.3)	
>70 yr	28 (21.1)	22 (19.6)	6 (28.6)	
Sex (no. of female, %)	58 (43.6)	49 (43.8)	9 (42.8)	0.94†
Race (no. of patients, %)				0.39†
Caucasian	125 (94)	105 (95.5)	20 (95)	
Hispanic	3 (2.3)	2 (1.8)	1 (4.7)	
African American	3 (2.4)	3 (2.7)	0 (0)	
Mean BMI (±SD)	29.5 ± 6.0	29.5 ± 6.25	29.2 ± 4.83	0.85*
Comorbidities (no. of patients, %)				
Smoking	23 (17.3)	94 (83.9)	16 (76.0)	0.39†
Vitamin D deficiency	31 (22.6)	22 (19.6)	9 (38.0)	0.063†
Mean vitamin D level (±SD)	27.8 ± 12.8	28.3 ± 12.6	25.2 ± 12.8	0.303*
Location (no. of patients, %)				0.69†
Cervical	65 (48.9)	53 (47.0)	12 (10.0)	
Lumbar	62 (46.6)	54 (48.2)	8 (38.1)	
Thoracic	6 (4.5)	5 (4.5)	1 (4.8)	
Mean no. of levels fused (±SD)	2.14 ± 1.9	2.0 ± 1.6	2.8 ± 3.2	0.186†
Approach (no. of patients, %)				0.446†
Anterior	39 (29.3)	34 (31.0)	5 (23.8)	
Posterior	87 (65.4)	71 (64.5)	16 (76.0)	
Combined	5 (3.8)	5 (4.5)	0 (0)	
Graft type (no. of patients, %)				0.808†
Allograft	54 (40.6)	46 (41.8)	8 (38.1)	
Autograft	19 (14.3)	15 (13.6)	4 (19.0)	
Both	58 (43.6)	49 (44.5)	9 (42.9)	
Revision (no. of patients,%)	32 (24.1)	28 (25.0)	4 (19.0)	0.558†
BMP use (no. of patients,%)	32 (24.1)	24 (21.6)	8 (38.0)	0.106†
Mean subjective scores (preoperative) (±SD)				
NDI	20.6 ± 9.3	21.1 ± 9.6	18.1 ± 7.6	0.415*
ODI	22.8 ± 8.8	23.3 ± 8.7	20.5 ± 9.3	0.416*
Mean follow-up time in mo (±SD)	16.0 ± 5.0	16.0 ± 5	15.0 ± 4.6	0.303‡

**T test of independence.*
†χ^2 test.
‡Mann-Whitney U Test.

TABLE 2. Multivariate Analysis Assessing Effect of Key Demographic and Independent Variables on Fusion Rates

Variable	Odds Ratio	Confidence Interval	*P*
Age	1.012	0.964, 1.062	0.64
Sex (female)	0.779	0.241, 2.521	0.677
Vitamin D deficiency	3.449	1.029, 11.561	0.045
Fusion length (no. of levels)	0.804	0.637, 1.016	0.067

Hosmer-Lemeshow test χ^2 *5.908, P = 0.657.*

normal vitamin D (>30 ng/mL) groups. We found a significantly longer estimated median time to fusion in the vitamin D-deficient group (<20 ng/mL) compared with the nondeficient group (>20 ng/mL) (12 *vs.* 6 mo, $P = 0.001$) (Figure 1, Table 3). When comparing the patients with vitamin D deficiency with those in the insufficient group (20–30 ng/mL) and those in the normal group (>30 ng/mL), we found a significantly longer estimated median time to fusion as well (12 *vs.* 8 *vs.* 6 mo, respectively, $P = 0.001$) (Figure 2, Table 4).

DISCUSSION

Approximately 1 quarter of the patients in this study (23%) demonstrated perioperative vitamin D deficiency. Multivariate analysis indicated that vitamin D deficiency was an independent predictor of nonunion after adjusting for age, sex, fusion length, location, graft type, and bone morphogenetic protein use. Furthermore, Kaplan-Meier survival analysis demonstrated a dose response to vitamin D levels in relation to time to fusion (Figure 2, Table 4).

Spinal fusion is the mainstay of treatment for multiple congenital and degenerative conditions; in fact, the number of patients undergoing lumbar fusion surgery increased 220% from 1990 to 2001.[12–14] Pseudarthrosis is one of the most common complications of lumbar spine surgery[15] and may represent a potentially treatable cause of delayed complication after spinal fusion and spinal instrumentation failure.[16] Pseudarthrosis rates range from 3% to 30%, depending on the operative approach and the number of spinal segments fused.[16–18] The risk factors for spinal pseudarthrosis and instrumentation failure include smoking, obesity, infection, corticosteroid use, and metabolic derangements, and it is often difficult to identify a single causative factor.[19] Poor BMD or osteoporosis is a known contributor to pseudarthrosis and instrumentation failure.[17]

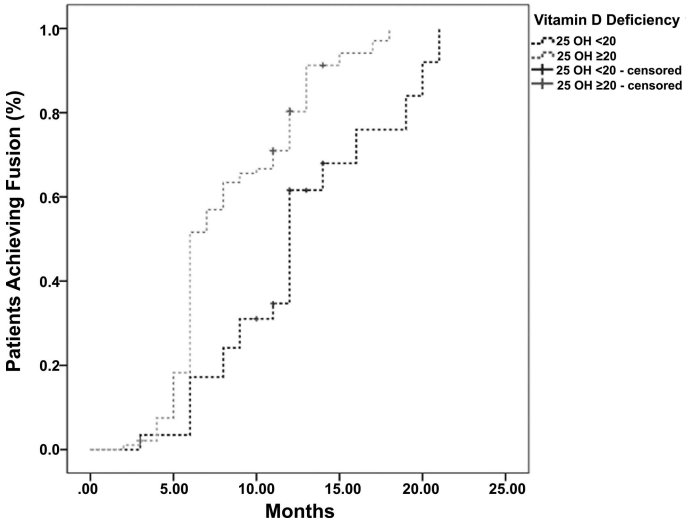

Figure 1. Kaplan-Meier graph demonstrating time to fusion for patients with low vitamin D levels (<20 ng/mL) and those with vitamin D levels >20 ng/mL. Graph illustrates 1–survival (i.e., time to fusion).

With an aging population, an increased prevalence of osteoporosis can be expected among patients presenting for surgery. This, in turn, is associated with a higher incidence of implant–bone interface failures and bone fractures. In the orthopaedic surgery literature, preventative treatment with vitamin D supplementation to ameliorate low BMD has been shown to reduce the incidence of hip fractures in postmenopausal women.[20,21] A similar strategy of preventative therapy may prove useful in patients undergoing elective spinal fusion procedures to increase fusion rates and reduce time to fusion.

We recently demonstrated a high rate of vitamin D deficiency in patients undergoing elective spinal fusion (30% deficient, 38.9% insufficient);[8] these findings are in concordance with the results of a 2011 study of vitamin D deficiency in the general population. Forrest *et al*[22] reported a 41.6% prevalence of vitamin D deficiency, with an average level of 19.9 ng/mL. Other studies have demonstrated vitamin D deficiency in patients with spinal pathology and undergoing spinal instrumentation. Kim *et al*[23] reported a 35.5% rate of hypovitaminosis D in 31 patients undergoing surgical therapy of lumbar spinal stenosis. Although specific risk factors were not elucidated, the authors reported an increase in vitamin D levels after surgical intervention. They suggested that this was driven by increased activity and healthier lifestyle adjustments after surgical intervention. Stoker *et al*[9] reported a 27% rate of vitamin D deficiency in 350 patients undergoing long-segment fusion/fixation. The authors demonstrated that risk factors for deficiency in an elective spinal surgery population included greater BMI, self-reported disability using the NDI or ODI scale, and lack of vitamin D supplementation.[9] The authors did not assess whether the fusion was achieved.

Vitamin D was shown to contribute to the consolidation of bone after grafting in a rat model, in which vitamin D levels were directly related to the density of the fusion mass. In their

TABLE 3. Median Estimated Time Until Fusion for Patients With Deficient and Normal Vitamin D Levels

Vitamin D Level (ng/mL)	Estimated Months Until Fusion	95% Confidence Interval
Deficient (<20)	12	11.215, 12.785
Normal (≥20)	6	5.47, 6.53
Overall	8	6.09, 9.91
Log Rank (Mantel-Cox) χ^2 13.557, $P < 0.001$.		

TABLE 4. Median Estimated Time Until Fusion for Patients Based on Vitamin D Level

Vitamin D Level (ng/mL)	Estimated Months Until Fusion	95% Confidence Interval
Deficient (<20)	12	11.215, 12.785
Insufficient (20–30)	8	6.102, 9.898
Normal (>30)	6	5.640, 6.360
Overall	8	6.09, 9.91
Log Rank (mantel-cox) χ^2 13.525, $P = 0.001$.		

study, Metzger *et al*[24] demonstrated a dose-dependent relationship between vitamin D and fusion rates assess by manual palpation, with adequate levels of vitamin D yielding stiffer fusion than inadequate levels ($P < 0.05$).

Vitamin D has been associated with improvement in back pain; Al Faraj *et al*[25] demonstrated that 95% of all patients and 100% of patients with vitamin D deficiency treated with supplementation had resolution of chronic low back pain 3 months after treatment. While these findings must be interpreted carefully, similar findings have been shown for patients with chronic back pain and failed spinal fusion surgery,[26–28] and thus the findings warrant consideration.

The potential value of these findings to spine surgeons is great. Low back pain, most commonly caused by lumbar spondylosis and degenerative spine disease, carries a lifetime prevalence ranging from 59% to 84%.[29] Parker *et al*[30] demonstrated that comprehensive medical management did not result in sustained improvement in pain, disability, or quality of life for patients with lumbar spondylolisthesis, stenosis, or disc herniation. With more scrutiny on less effective and more costly procedures in spine surgery, potential avenues for improving outcomes and decreasing reoperation rates should be explored. Among spine surgeons, the assessment of vitamin D status is not commonplace. In 2009, Diapola *et al*[31] stated that just 12% of spine surgeons do metabolic testing, including serum levels of vitamin D, prior to fusion surgery and only 20% as part of a pseudarthrosis work-up.

These findings indicate that a prospective study of patients undergoing spinal fusion to determine the impact of vitamin D supplementation and its relationship to fusion, pseudarthrosis, and instrumentation failure is necessary. Vitamin D supplementation can be accomplished in a cost-effective manner at between $0.21 and $1.46 a week (http://redbook.com/redbook/online/). Conversely, the 2-year cost of revision surgery after pseudarthrosis in the lumbar spine was recently estimated at $28,069.[32]

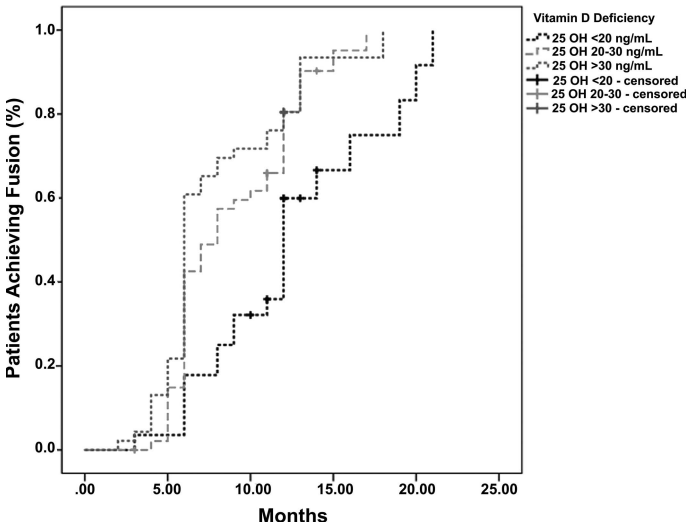

Figure 2. Kaplan-Meier graph demonstrating time to fusion for patients with deficient vitamin D levels (<20 ng/mL), insufficient vitamin D levels (20–30 ng/mL), and normal vitamin D levels (>20 ng/mL). Graph illustrates 1–survival (i.e., time to fusion).

Limitations

This study is limited by a somewhat small cohort size. Our initial cohort included 234 patients in whom perioperative vitamin D levels were assessed; but 43% of the cohort was lost to follow-up. Ultimately, the size of the vitamin D-deficient patient group was 31 patients. Furthermore, the 1-year follow-up is short. It is possible that additional patients would have achieved fusion with a longer follow-up period. Thus, longer-term follow-up is needed to elucidate the long-term effects of vitamin D on bony fusion. Additionally, true time to fusion can be difficult to ascertain with specified follow-up intervals (6 mo, 12 mo, *etc.*), thus there is inherent bias that may overestimate time to fusion in a certain percentage of patients, although this overestimation should be similar in all groups.

Another limitation of the study is the absence of follow-up serum vitamin D levels on the patient cohort. It would be beneficial to follow the trend of vitamin D levels in deficient patients as a marker for bony health and response to supplementation. The use of vitamin D supplementation after fusion was outside of the scope of this study, but our results indicate it might prove to be a worthwhile endeavor.

Dual-energy X-ray absorptiometry (DEXA) scanning is not routine procedure at our institution, and a very small number of patients had DEXA scans available; in this small subset there was no greater association with vitamin D deficiency.

Finally, it can be inappropriate to apply findings from a study at a single institution more broadly. Although there is inherent homogeneity in patients treated at a single institution with presumably similar levels of elevation and exposure to sunlight, we think there was significant heterogeneity in our patient population, making this information useful for spine surgeons treating a variety of spinal disorders and pathology.

CONCLUSION

Despite these limitations, this report does provide useful insight into the potential effect of vitamin D on rates of fusion and time to fusion. Our results showed that vitamin D levels were associated with a lower fusion rate and longer time to fusion. This is the first report of the association of vitamin D deficiency with fusion rates and increased time to fusion. The results offer insight into the importance of the metabolic milieu of bony fusion as well as potential for therapeutic intervention.

➢ Key Points

- ❑ Vitamin D is critical to bone health and may promote fusion.
- ❑ Perioperative vitamin D levels may affect fusion rate and time to fusion.
- ❑ Vitamin D supplementation may represent a potential therapeutic intervention to improve fusion rates.

Acknowledgments

The authors thank Kristin Kraus, MSc, for editorial assistance in preparing this paper and Richard H. Schmidt, MD, PhD, and Joel D. MacDonald, MD, for their participation in this study. V.M.R. and J.G. contributed equally to this work.

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