

Improvement of Pain, Sleep, and Quality of Life in Chronic Pain Patients With Vitamin D Supplementation

Wei Huang, MD, PhD,*†‡ Shivani Shah, DO,† Qi Long, PhD,‡
Alicia K. Crankshaw, MD,† and Vin Tangpricha, MD, PhD§||

Objectives: To evaluate the effects of vitamin D supplementation in outpatient veterans with multiple areas of chronic pain.

Methods: A case series was performed as an outpatient vitamin D supplementation quality improvement project. A total of 28 US veterans with multiple areas of chronic pain and low serum 25-hydroxyvitamin D [25(OH)D] (< 30 ng/mL) concentrations at baseline were identified in a major Veterans Affairs Medical Center from May 2009 till November 2010. They were supplemented with vitamin D 1200 IU daily if serum 25(OH)D was in the insufficient range (20 to 29 ng/mL) or 50,000 IU weekly if serum 25(OH)D was in the deficient range (< 20 ng/mL). Standardized outcome measures were assessed before and after supplementation, including pain assessed by the 0 to 10 pain score and the bodily pain domain score of the Veterans Rand 36 item, sleep by the Pittsburgh Sleep Quality Index, and quality of life (QoL) by the Veterans Rand 36 item.

Results: Participants reported no side effects during the study. Relative to baseline, pain, sleep, and QoL all improved except for role-functioning emotional. The improvements remained significant in pain score ($P < 0.001$), sleep latency ($P = 0.019$), sleep duration ($P = 0.012$), bodily pain ($P = 0.014$), general health ($P = 0.006$), vitality ($P = 0.048$), and social functioning ($P = 0.017$) after controlling for age, sex, race, body mass index, season, baseline serum 25(OH)D concentration subgroup, and whether or not participants received additional procedural intervention during the supplementation period.

Conclusions: Standardized vitamin D supplementation in veterans with multiple areas of chronic pain can be effective in improving their pain levels, sleep, and various aspects of QoL.

Key Words: vitamin D, chronic pain, sleep, quality of life, quality improvement

(*Clin J Pain* 2012;00:000–000)

Chronic pain is a common condition presenting to physicians for treatment and has been reported to have a prevalence of up to 40% in the western adult population.^{1,2}

Received for publication August 27, 2011; accepted March 13, 2012. From the *Physical Medicine and Rehabilitation; ||Geriatrics, Extended Care Service Line, Atlanta VA Medical Center, Decatur; †Department of Rehabilitation Medicine; §Department of Medicine, Division of Endocrinology, Metabolism & Lipids, Emory University School of Medicine; and ‡Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, GA.

Supported in part by US Department of Veterans Affairs Rehabilitation Research NW Washington, DC and Development Career Development Award Level II (W.H.) (B6924W). The authors declare no conflict of interest.

Reprints: Wei Huang, MD, PhD, PM&R/Geriatrics, Extended Care, and Rehabilitation Service Line, 508/11B, Atlanta VA Medical Center, 1670 Clairmont Road, Decatur, GA 30033 (e-mail: whuang4@emory.edu).

Copyright © 2012 by Lippincott Williams & Wilkins

The underlying mechanisms leading to chronic pain are complex, with various theories suggesting physiological, immunologic, genetic, psychological, and psychosocial influences.^{3–6} The health care cost associated with chronic pain treatment is paramount and compounded by the cost of wage replacement and welfare programs for those who do not work because of pain.⁷ Developing alternative and complementary treatment options that are low risk, of low cost, and effective can improve these patients' quality of life (QoL) and decrease health care expenditure.

Vitamin D may exert anatomic and immunologic influences on pain manifestation.^{8,9} Vitamin D deficiency has been reported to be associated with higher risk of chronic pain,^{8,10–14} although the findings are still controversial.¹⁵ Vitamin D supplementation has a favorable risk profile, is widely available, and is inexpensive, making it an appealing alternative and complementary treatment for chronic pain. Prior studies evaluating the use of vitamin D in chronic pain have focused on those with osteoporosis,^{16–19} rheumatoid conditions,²⁰ or very low serum 25-hydroxyvitamin D [25(OH)D] concentrations.^{21,22} Studies using the visual analog pain scores as the primary or solitary outcome measure have shown mixed results in chronic pain patients when evaluating the impact of vitamin D supplementation.^{16,17,20,21,23–26} To measure treatment success for chronic pain, QoL assessments are not only important but also appropriate and reliable.^{27,28} Additional standardized measurements for not only pain but also QoL, such as the Veterans Rand 36 item (VR-36), are indicated to better capture the overall improvements in these patients after intervention.

Sleep difficulties and chronic pain are interrelated.^{29,30} Vitamin D supplementation has been demonstrated to resolve hypersomnia in 1 case report,³¹ but the effects of vitamin D on sleep have not been examined in other studies. Subjective measures of sleep, for instance by the Pittsburgh Sleep Quality Index (PSQI), will provide important data before using objective measures to evaluate sleep outcome in such populations. The aim of this study was to gain preliminary knowledge about the effects of vitamin D supplementation on self-reported pain, QoL, and sleep in patients seen in an outpatient setting, who present with multiple areas of chronic pain and low serum concentrations of 25(OH)D.

METHODS

Study Design

This study was designed prospectively as a quality improvement project aiming to standardize clinicians' practice regarding vitamin D supplementation and chronic pain and to allow collection of certain monitoring data at the same time, which are otherwise not regularly collected

in clinics. It was later retrospectively analyzed as a case series by medical record review. The study protocol was reviewed and approved by the Institutional Review Board of Emory University and Atlanta Veterans Affairs Medical Center (VAMC) Research and Development Committee.

Study Population

This study was carried out in a physiatry pain clinic and a primary care clinic in a major VAMC in southeast United States. All patients in these clinics receive regular medical care and pain management. Pain specialists or primary care providers at these clinics, as part of our quality improvement project, test the serum 25(OH)D concentration in patients presenting with 2 or more areas of chronic pain that were refractory to various treatment modalities, including physical or occupational therapies, topical treatments, medications, and invasive injections. Chronic pain was defined according to the American Society of Interventional Pain Physicians as “pain that persists 6 months after an injury and beyond the usual course of an acute disease or a reasonable time for a comparable injury to heal,” which “may continue in the presence or absence of demonstrable pathology; may not be amenable to routine pain control methods.”³² The areas of pain were assessed by the number of pain areas according to anatomic locations, including head, neck, shoulder, elbow, wrist, hand, mid back, low back, tailbone, hip, knee, ankle, and foot.

Those patients with serum 25(OH)D concentration below 30 ng/mL were identified by medical record review and further divided into 2 subgroups⁹: (1) insufficient (INS) with serum 25(OH)D concentration at 20 to 29 ng/mL; and (2) deficient (DEF) with serum 25(OH)D concentration at < 20 ng/mL. We excluded patients with hypocalcemia, signs of osteomalacia on physical examination, low bone mineral density by dual-energy x-ray absorptiometry, with *t* score lower than -1, history of primary hyperparathyroidism, history of kidney stones and hypercalcemia, or other contributing or associated endocrinopathy. We further excluded those patients who did not complete 3 months of vitamin D supplementation due to either failure to refill supplementation monthly or not being compliant to scheduled dosing and those who did not wish to complete presupplementation and postsupplementation questionnaires, the VR-36, and the PSQI.

Intervention

The vitamin D supplementation schedule was standardized according to the presupplementation serum 25(OH)D subgroups. The INS subgroup was supplemented with cholecalciferol (D₃) 1200 IU daily, and the DEF subgroup was supplemented with ergocalciferol (D₂) 50,000 IU weekly. The availability of vitamin D (D₂ or D₃) at certain dosages was limited by the VA formulary. Both medications are well absorbed from the gastrointestinal tract when taken orally and can raise serum 25(OH)D concentrations to steady state within 2 months.³³ Thus, per os (po, taking the medication by mouth) route was selected for its convenience in delivery and cost efficiency. The supplementation duration was 3 months.

Primary Outcome Measures

Presupplementation and postsupplementation standardized assessments, including a 0 to 10 pain score (see Appendix) based on the widely used clinical numerical rating pain scale,³⁴ VR-36, and PSQI, were administered by W.H., S.S.,

or A.K.C., mostly over the phone (89.3%) but with a few face-to-face sessions, according to the patients' convenience.

VR-36³⁵

The VR-36 is a validated standardized questionnaire to evaluate health-related QoL. It was developed and modified from the original RAND Version of the 36-item Health Survey version 1.0, known as MOS SF-36, for improved responses in the veteran's population.^{36,37} The 8 multi-item domains of the VR-36 include physical functioning (the extent to which health limits typical daily activities such as climbing stairs), role-functioning physical (the extent to which physical health interferes with work or other activities), bodily pain (the intensity of pain and extent to which pain interferes with normal activity), general health (personal evaluation of current health and health outlook), vitality (the frequency of feeling energetic rather than feeling tired and worn out), social functioning (the extent to which physical health or emotional problems interfere with normal social activities), role-functioning emotional (the extent to which emotional problems interfere with work or other activities), and mental health (the frequency of experiencing anxiety, happiness, etc.). Each scale is scored 0 to 100, with a higher score indicating better perceived QoL. They are further summarized into 2 standardized component scales, physical and mental component scales, scored using a linear *t* score transformation that was normed to a general US population. These provide an important contrast between physical and psychological health status.³⁸

PSQI³⁹

The PSQI is a validated standardized questionnaire to assess subjective sleep quality and quantitative sleep-wake parameters over the preceding month. Responses to 19 items are scaled onto 7 component scores, which are totaled to provide a global PSQI score ranging from 0 to 21, with higher scores representing worse sleep. A global score of 5 or greater indicates sleep difficulties. According to the answers to question 2 “how long has it usually taken you to fall asleep each night,” question 4 “how many hours of actual sleep did you get at night,” question 4 along with question 1 “what time have you usually gone to bed at night,” and question 3 “what time have you usually gotten up in the morning,” sleep latency, sleep duration, and sleep efficiency were derived, respectively.

Secondary Outcome Measures

Serum 25(OH)D concentrations were tested with liquid chromatography-mass spectrometry assay at Quest Diagnostics (Chantilly, VA) within 1 week prior and 2 weeks after 3 months of vitamin D supplementation; number of pain areas and number of pain medications by patients' self-report were monitored before and after supplementation.

Statistical Analysis

Demographic and baseline (before supplementation) outcome measures of the study participants were compared using Wilcoxon rank sum tests for continuous variables and ordinal variables, and using Fisher exact tests for nominal categorical variables. Wilcoxon signed-rank tests were used to test whether the sleep and QoL measures changed from presupplementation to postsupplementation in the overall study population and in subgroups defined by

the presupplementation serum 25(OH)D concentrations. Wilcoxon rank sum tests were used to compare change from presupplementation to postsupplementation between the INS and DEF subgroups.

Generalized estimation equations,⁴⁰ which included an indicator variable for time of measurement (ie, 0 for presupplementation and 1 for postsupplementation), were used to further assess the adjusted changes from presupplementation to postsupplementation, represented by the regression coefficient for the time variable, while controlling for potential confounders including age, sex (male, female), race (African American, white), body mass index (BMI), season of the year at initial presentation of each participant, presupplementation serum 25(OH)D concentration subgroups (INS, DEF), and whether or not the participants received additional procedural intervention (yes, no). Participants receiving any procedural intervention such as intra-articular steroid injections, epidural steroid injections, or trigger point injections during the period of vitamin D supplementation would be in the “Yes” group.

Backward model selection was performed, in particular, to determine whether the improvement of all these outcome measures from presupplementation to postsupplementation is different between INS and DEF subgroups, and between participants who received additional procedural intervention and those who did not, by testing the interaction term between time of measurement and the presupplementation serum 25(OH)D concentration subgroup, and the interaction term between time of measurement and additional procedural intervention category, respectively. Findings with $P < 0.05$ were considered statistically significant.

RESULTS

A total of 90 patients with multiple areas of chronic pain were referred for serum 25(OH)D testing during the period. Among the 82 patients who completed laboratory testing, 46 (56.1%) were identified to have a baseline serum 25(OH)D concentration < 30 ng/mL. Four patients were excluded for not completing 3 months of vitamin D supplementation. Other reasons for loss of patients were loss of contact, lack of follow-up laboratories within the time frame reasonable for our report, pharmacy’s mistakes in refill, and patients’ refusal to answer presupplementation or postsupplementation questionnaires ($n = 14$). Twenty-eight participants were included in this final report.

Demographics

Twenty-three of the 28 participants were referred from the pain clinic, whereas the rest were referred from the primary care clinic. The mean age of the participants was 46.2 ± 10.8 years, which was within the main age range of veterans typically receiving care at VAMC.⁴¹ They were majority of men ($n = 18$), although the percentage (64.3%) was lower than the usual composition of men among veterans (about 90%).⁴¹ The percentage of African Americans was 71.4% ($n = 20$), likely reflecting risk of vitamin D insufficiency in certain ethnic groups as speculated in prior studies.⁴²⁻⁴⁴ They tended to be obese with an average BMI of 31.12 ± 6.02 kg/m². When comparing the subgroups on the basis of baseline serum 25(OH)D concentration (INS vs. DEF), there was no statistically significant difference in these demographics (Table 1).

TABLE 1. Demographic and Baseline Pain, Sleep, and Quality-of-life Measures of the Study Participants Categorized by Presupplementation Serum 25-hydroxyvitamin D Concentrations: INS Versus DEF

	INS (n = 15)	DEF (n = 13)	P*
Age (mean ± SD)	47.55 ± 12.00	44.58 ± 9.46	0.50
Male sex, n (%)	11 (73.3)	7 (53.8)	0.43
African American, n (%)	9 (60.0)	11 (84.6)	0.22
BMI (mean ± SD)	30.38 ± 5.89	31.98 ± 6.29	0.50
Pain (mean ± SD)			
Pain score (0-10)	7.07 ± 1.10	7.15 ± 1.46	0.98
No. pain areas	3.93 ± 1.16	4.08 ± 0.86	0.86
No. pain medications	2.00 ± 1.77	2.38 ± 1.39	0.60
Sleep (mean ± SD)			
Global PSQI score	12.27 ± 5.55	14.85 ± 3.83	0.22
Sleep latency (min)	41.61 ± 48.21	94.81 ± 52.15	0.006
Sleep duration (h)	5.33 ± 1.88	3.73 ± 1.41	0.025
Sleep efficiency (%)	66.97 ± 23.7	52.61 ± 25.70	0.17
VR-36 scores (mean ± SD)			
Physical functioning	35.00 ± 27.97	30.77 ± 21.00	0.87
Role-functioning physical	29.58 ± 30.02	27.88 ± 20.35	0.78
Bodily pain	27.00 ± 24.64	27.08 ± 20.71	0.71
General health	34.33 ± 22.89	33.31 ± 16.33	0.94
Vitality	27.89 ± 17.56	21.54 ± 19.73	0.32
Social functioning	40.83 ± 33.23	27.88 ± 31.11	0.32
Role-functioning emotional	57.22 ± 35.05	39.1 ± 29.73	0.17
Mental health	57.87 ± 25.78	37.23 ± 27.05	0.053
Physical component scale	26.44 ± 11.38	28.78 ± 6.60	0.25
Emotional component scale	41.79 ± 14.83	31.31 ± 14.07	0.088

*Wilcoxon rank sum tests were used for continuous variables and ordinal variables, and Fisher exact tests were used for nominal categorical variables. Findings with $P < 0.05$ were considered statistically significant.

Numbers in italic indicate significant difference.

BMI indicates body mass index; DEF, deficient subgroup; INS, insufficient subgroup; PSQI, Pittsburgh Sleep Quality Index; VR-36, Veterans Rand 36 item.

Serum 25(OH)D Response to Vitamin D Supplementation

At presupplementation, the mean serum 25(OH)D concentration was 18.57 ± 5.42 ng/mL. It improved significantly to 26.00 ± 8.38 ng/mL after vitamin D supplementation ($P = 0.006$) (Table 2). The improvement was most significant in the DEF subgroup ($P = 0.008$) but not in the INS subgroup; although the magnitude in improvement of serum 25(OH)D concentrations was not statistically significant between the subgroups ($P = 0.32$). After controlling for potential confounders, the overall improvements from presupplementation to postsupplementation remained significant in all groups ($P < 0.001$).

Pain Response to Vitamin D Supplementation

All participants had baseline chronic pain in 2 or more areas; 64.3% of them had pain in > 3 areas. Their mean 0 to 10 pain score was 7.11 ± 1.26 . Two of the participants (7.1%) did not use any pain medication, whereas 4 participants (14.3%) used > 3 pain medications. Their bodily pain assessed by the VR-36 was 27.04 ± 22.48 . According to the participants’ presupplemental serum 25(OH)D concentration, those with insufficient vitamin D levels had similar pain manifestations as those with deficient levels, including 0 to 10 pain score, bodily pain domain in the

TABLE 2. Participants' Outcome Measures (Mean ± SD) at Presupplementation and Postsupplementation of Vitamin D

INS (n = 15)* DEF (n = 13)*	Presupplementation (n = 28)*	Postsupplementation (n = 28)*	Change From Pre to Post	<i>P</i> †	<i>P</i> ‡
Serum 25(OH)D	18.57 ± 5.42	26.00 ± 8.38	9.00 ± 9.45	0.006	< 0.001
INS	22.73 ± 1.83	29.60 ± 11.67	6.00 ± 11.42	0.42	
DEF	13.77 ± 3.94	24.00 ± 5.79	10.67 ± 8.43	0.008	
10-point pain score	7.11 ± 1.26	5.68 ± 1.59	-1.43 ± 1.00	< 0.001	< 0.001
INS	7.07 ± 1.10	5.73 ± 1.75	-1.33 ± 1.05	0.003	
DEF	7.15 ± 1.46	5.62 ± 1.45	-1.54 ± 0.97	0.003	
Global PSQI score	13.46 ± 4.92	12.22 ± 4.61	-1.44 ± 1.80	0.001	0.030
INS	12.27 ± 5.55	11.29 ± 4.66	-1.29 ± 1.54	0.019	
DEF	14.85 ± 3.83	13.23 ± 4.51	-1.62 ± 2.10	0.012	
Sleep latency (min)	67.22 ± 56.13	57.86 ± 44.03	-8.89 ± 19.32	0.026	0.019
INS	41.61 ± 48.21	39.83 ± 39.05	-2.14 ± 9.7	0.89	
DEF	94.81 ± 52.15	78.65 ± 41.33	-16.15 ± 24.42	0.030	
Sleep duration (h)	4.59 ± 1.84	5.30 ± 1.57	0.71 ± 0.83	< 0.001	0.012
INS	5.33 ± 1.88	5.90 ± 1.55	0.57 ± 0.78	0.013	
DEF	3.73 ± 1.41	4.62 ± 1.33	0.88 ± 0.89	0.008	
Sleep efficiency (%)	59.79 ± 25.31	66.62 ± 18.61	7.33 ± 16.86	0.015	0.054
INS	66.97 ± 23.7	70.34 ± 17.76	4.94 ± 16.82	0.17	
DEF	52.61 ± 25.70	62.33 ± 19.34	9.73 ± 17.23	0.053	
Physical functioning	33.04 ± 24.62	45.36 ± 23.96	12.32 ± 9.57	< 0.001	0.079
INS	35.00 ± 27.97	47.00 ± 25.06	12.00 ± 9.78	0.001	
DEF	30.77 ± 21.00	43.46 ± 23.49	12.69 ± 9.71	0.004	
Role-functioning physical	28.79 ± 25.53	35.71 ± 22.56	6.92 ± 8.56	0.002	0.395
INS	29.58 ± 30.02	37.92 ± 26.04	8.33 ± 8.41	0.009	
DEF	27.88 ± 20.35	33.17 ± 18.47	5.29 ± 8.78	0.077	
Bodily pain	27.04 ± 22.48	36.64 ± 17.29	9.61 ± 14.52	0.002	0.014
INS	27.00 ± 24.64	37.73 ± 18.82	10.73 ± 9.67	0.006	
DEF	27.08 ± 20.71	35.38 ± 16.01	8.31 ± 19.02	0.091	
General health	33.86 ± 19.79	40.96 ± 18.12	7.11 ± 9.23	0.001	0.006
INS	34.33 ± 22.89	43.80 ± 18.98	9.47 ± 8.9	0.003	
DEF	33.31 ± 16.33	37.69 ± 17.23	4.38 ± 9.17	0.138	
Vitality	24.94 ± 18.53	33.75 ± 19.94	8.81 ± 11.97	0.001	0.048
INS	27.89 ± 17.56	39.33 ± 18.79	11.44 ± 12.41	0.006	
DEF	21.54 ± 19.73	27.31 ± 19.96	5.77 ± 11.15	0.101	
Social functioning	34.82 ± 32.34	45.54 ± 26.4	10.71 ± 10.04	< 0.001	0.017
INS	40.83 ± 33.23	50.83 ± 26.92	10.00 ± 10.77	0.006	
DEF	27.88 ± 31.11	39.42 ± 25.44	11.54 ± 9.49	0.007	
Role-functioning emotional	48.81 ± 33.39	51.79 ± 31.86	2.98 ± 15.91	0.132	0.500
INS	57.22 ± 35.05	58.33 ± 35.07	1.11 ± 19.38	0.552	
DEF	39.10 ± 29.73	44.23 ± 27.09	5.13 ± 11.04	0.122	
Mental health	48.29 ± 27.92	53.43 ± 23.00	5.14 ± 8.77	0.006	0.252
INS	57.87 ± 25.78	61.60 ± 20.99	3.73 ± 7.48	0.092	
DEF	37.23 ± 27.05	44.00 ± 22.27	6.77 ± 10.12	0.043	
Physical component scale	27.53 ± 9.38	31.68 ± 8.45	4.16 ± 3.67	< 0.001	0.056
INS	26.44 ± 11.38	31.21 ± 9.82	4.77 ± 3.08	< 0.001	
DEF	28.78 ± 6.60	32.23 ± 6.88	3.44 ± 4.27	0.008	
Mental component scale	36.92 ± 15.18	38.80 ± 13.05	1.88 ± 5.17	0.048	0.279
INS	41.79 ± 14.83	43.31 ± 12.71	1.52 ± 5.98	0.229	
DEF	31.31 ± 14.07	33.60 ± 11.82	2.29 ± 4.26	0.127	

In subgroup analysis, the participants were categorized into 2 subgroups according to baseline serum 25(OH)D concentrations: insufficient (INS: 20 to 29 ng/mL) and deficient (DEF: <20 ng/mL).

*The number of participants varied slightly for different outcomes before and after supplementation due to missing data.

†Wilcoxon signed-rank tests were performed to test whether the change from presupplementation to postsupplementation is different from 0. Findings with *P* < 0.05 were considered statistically significant.

‡Generalized estimation equation analysis was used to test whether the change from presupplementation to postsupplementation is different from 0, while controlling for age, sex, race, season, body mass index, presupplementation serum 25(OH)D concentration subgroup, and whether or not the participants received additional procedural intervention during the supplementation period. Findings with *P* < 0.05 were considered statistically significant.

Numbers in italic indicate significant difference.

DEF indicates deficient subgroup; INS, insufficient subgroup; PSQI, Pittsburgh Sleep Quality Index; 25(OH)D, 25-hydroxyvitamin D.

VR-36, number of pain areas, and number of pain medications (Table 1).

After vitamin D supplementation, the percentage of participants with >3 pain areas decreased to 53.6% (*P* = 0.0006). Their mean 0 to 10 pain score decreased to 5.68 ± 1.59, which was statistically significant with or

without controlling for potential confounders (*P* < 0.001). After supplementation, the percentage of participants not using any pain medication increased to 10.7%, and the percentage using >3 pain medications decreased to 10.7% (*P* = 0.0022). The bodily pain assessed by the VR-36 improved to 36.64 ± 17.29 (*P* = 0.002), which remained

significant after controlling for potential confounders ($P = 0.014$). The improvements in these pain characteristics were similar between the 25(OH)D subgroups, and between participants who did and those who did not receive additional procedural intervention during the vitamin D supplementation period.

Sleep Response to Vitamin D Supplementation

At presupplementation, all participants reported sleep difficulties. Their mean global PSQI score was 8.46 points above normal, with average sleep latency of over an hour, average sleep duration slightly over 4½ hours, and average sleep efficiency < 60%. The group with deficient presupplemental serum 25(OH)D concentration presented with a worse sleep pattern, that is significantly longer sleep latency ($P = 0.006$) and shorter sleep duration ($P = 0.025$) (Table 1).

All sleep outcome measures improved after vitamin D supplementation, and remained statistically significant after controlling for potential confounders except sleep efficiency, which became borderline significant (Table 2). The magnitudes of sleep improvement in latency, duration, and efficiency were all larger in the deficient subgroup (Table 2); however, the difference in improvements between the 25(OH)D subgroups was not statistically significant except sleep latency ($P = 0.02$). The difference in improvement between participants who did and those who did not receive additional procedural intervention during the vitamin D supplementation period was similar.

QoL Response to Vitamin D Therapy

At presupplementation, the health-related QoL assessed by the other 7 domains besides bodily pain in the VR-36 had their mean scores mostly < 40 (Table 2). The participants with presupplemental serum 25(OH)D concentration at the deficiency level had worse functional status, although it was statistically not significant (Table 1).

All these areas related to QoL improved significantly, except for role-functioning emotional, after vitamin D supplementation (Table 2, Fig. 1). The 2 summary component scale scores also improved significantly but more physically than mentally. Subgroup analysis showed more substantial

QoL improvements in the INS subgroup for physically related assessments and more substantial QoL improvements in the DEF subgroup for emotionally related assessments; however, the difference in improvements between the subgroups was not statistically significant. QoL improvements in participants who did and those who did not receive additional procedural intervention during the vitamin D supplementation period were statistically similar. After controlling for potential confounders, the improvements in QoL remained significant in general health, vitality, and social functioning and were borderline significant in physical functioning and the physical component scale.

DISCUSSION

We report a prospective case series of patients with chronic pain and low serum 25(OH)D concentrations (< 30 ng/mL) at baseline, who received 3 months of vitamin D supplementation as part of a quality improvement project. After supplementation, their mean serum 25(OH)D concentration improved by almost 40%. Associated with this increase, the participants reported a significant decrease in pain level, number of pain areas, and pain medication use, and improvement in sleep and health-related QoL.

In prior studies, the response to vitamin D has been inconsistent possibly due to the use of the 0 to 10 pain score as the main or solitary outcome measure.¹⁵ In contrast to these prior studies, our study not only included the standard 0 to 10 pain score as a pain outcome, but also included other pain assessments, that is bodily pain domain by a QoL questionnaire (the VR-36), number of pain areas, and number of pain medications used, providing a more comprehensive evaluation of pain. Improvements in all these areas in our study participants further support the fact that vitamin D supplementation is associated with a reduction in pain manifestations, even in patients with chronic pain deemed refractory to other conventional treatments. Such improvements were not dependent on age, sex, race, BMI, season, presupplementation serum 25(OH)D concentration subgroup, or whether or not the participants received additional procedural interventions. Along with improvements in pain,

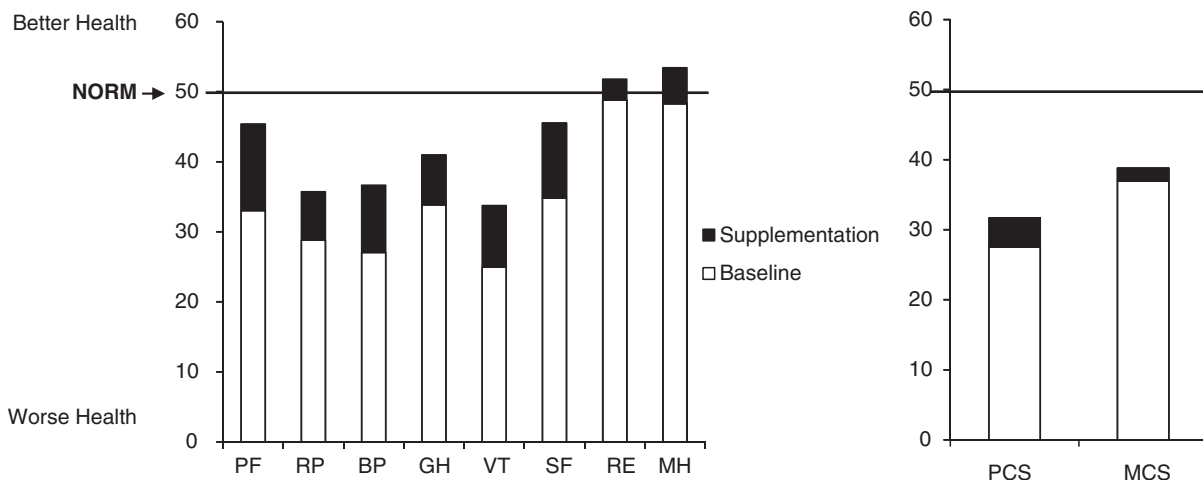


FIGURE 1. Health-related quality-of-life outcome assessed by the Veterans Rand 36 item before and after vitamin D supplementation in outpatient military veterans with multiple areas of pain (n=28), as compared with population norm. BP indicates bodily pain; GH, general health; MCS, mental component scale; MH, mental health; PCS, physical component scale; PF, physical functioning; RE, role-functioning emotional; RP, role-functioning physical; SF, social functioning; VT, vitality.

our study participants also had improvements in health-related QoL, similar to findings in a previous study using a 1-time bolus dose of vitamin D through either the per os or parenteral route in the elderly.⁴⁵ In comparison, our follow-up period was longer than the prior study (at least 3 mo vs. 4 wk), indicating possible sustained effects of vitamin D in improving pain and QoL.

We found that lower vitamin D status at baseline was associated with more difficulty in sleep. Prior studies on vitamin D supplementation failed to examine the sleep component in chronic pain patients, although chronic pain and sleep difficulties are closely related.⁴⁶ Our participants achieved significant sleep improvements after vitamin D supplementation with decreased sleep latency, improved sleep efficiency, and approximately 45 minutes longer sleep duration. These changes remained significant or borderline significant even after controlling for potential confounders. The positive interaction of improved sleep and alleviated pain with improved vitamin D status merits awareness in clinical practice. The relationship between vitamin D status and sleep is still unknown at neural or humoral levels and requires further investigation. Future objective sleep measures in vitamin D studies are warranted for revealing the possible underlying mechanism.

The duration of the use of oral vitamin D supplementation in our study was limited to 3 months. The improvements were significant using such minimal intervention with vitamin D. Our supplementation dosages of vitamin D were determined according to baseline serum 25(OH)D, mainly out of safety concerns. There have been no reported major side effects during the supplementation period. Although our study showed more significant improvement of serum 25(OH)D concentration with weekly mega dose, we are not certain whether weekly administration of vitamin D confers an advantage over daily administration of vitamin D in participants with chronic pain. After supplementation, 57.1% of tested study participants improved their serum 25(OH)D concentrations from deficient to insufficient or from insufficient to normal; however, 21% remained deficient and 50% remained insufficient. Higher and/or more prolonged dosing of vitamin D is likely necessary to achieve vitamin D sufficiency in all participants. The long-term efficacy and safety of vitamin D supplementation in participants with chronic pain requires further investigation, preferably using the same type of supplementation, as our selection was limited by the medications available in our VA formulary.

Prior studies suggested that homebound elderly people, people with pigmented skin, people who avoid the sun due to cultural and social reasons, people who live above and below latitudes of 35 degrees during winter, and patients with gastrointestinal malabsorption are at risk for developing vitamin D deficiency.¹⁴ Our study investigated another population—veterans with multiple areas of chronic pain, a population which is limited in mobility and has difficulty with outdoor activity due to pain. Therefore, we cannot be certain whether their pain conditions lead to vitamin D deficiency or whether vitamin D deficiency leads to their pain conditions. Long-term prospective studies will be necessary to examine this potential cause and effect relationship to provide further evidence that vitamin D has a role in the improvement of chronic pain in these patients.

Because this is a preliminary study based on a quality improvement project, we did not have a control group. Our study participants continued to receive regular medical care and pain management during the vitamin D supplementa-

tion period. As they were refractory to these treatments at baseline, this could partially serve as a within-participant control. We categorized the participants into 2 groups, with or without additional procedural interventions, and used regression analysis to control for this potential confounder and found no statistical difference between the groups. The current study is subject to potential selection bias due to loss of participants ($n = 18$) and small final sample size, and caution is needed when the results are generalized to a wider population. The small sample size in this preliminary study ($n = 28$) also limits our power to detect association between improvement of outcome measures and other risk factors that may be significant. Despite this limitation, the results from our study support the value of identifying low vitamin D status in patients with multiple areas of chronic pain that is refractory to treatment, and that supplementation of vitamin D in these patients leads to alleviated pain and improved sleep and QoL.

CONCLUSIONS

Our preliminary study demonstrated that standardized vitamin D supplementation in veterans with multiple areas of chronic pain can be effective in alleviating their pain and improving sleep, and various aspects of QoL. Longer term studies with larger sample size, preferably among both veterans and civilians, using objective and subjective outcome measures, in a randomized controlled clinical trial with different supplementation schedules, would provide better understanding of the effects and limitations of vitamin D supplementation in this population and reveal its possible underlying mechanisms.

ACKNOWLEDGMENT

The authors thank Dr Theodore M. Johnson II MD, MPH, Geriatrics, Extended Care Service Line, Atlanta VA Medical Center, Division of Geriatric Medicine and Gerontology, Department of Medicine, Emory University School of Medicine, Atlanta, GA, for manuscript review and provision of valuable feedback for its improvement.

APPENDIX

0 to 10 pain score: a pain score from 0 to 10 was reported by patients after the following definitions were explained to them.

0 as “No pain”;

1 as “Minimal discomfort that is easily forgotten, and no medication is considered”;

2 as “Minor aches, but pain medication is not needed as long as you are concentrating or busy with something else”;

3 as “Pain interferes with activity, but over-the-counter pain relievers (such as Advil, Aleve, or Tylenol) relieve it completely for 3 to 4 hours”;

4 as “Over-the-counter pain relievers help enough to allow you to forget the pain as long as you are concentrating or busy with something else”;

5 as “Even with over-the-counter medications, pain is noticed and it impedes your activity”;

6 as “Activities cannot be performed because over-the-counter analgesics are not controlling pain. Prescription pain relievers are needed to allow activity to continue without thinking about the pain”;

7 as “With prescription pain relievers and some effort, you can still perform activities, but pain is affecting your concentration”;

8 as “Activity is severely limited even with prescription pain relievers, and it is difficult to even read or carry on a conversation”;

9 as “Medications are not helping the pain, and physical activity is impossible”;

10 as “Pain is incapacitating despite narcotics and other prescription medications, and you are unable to do anything but cry or moan uncontrollably.”

REFERENCES

- Elliott AM, Smith BH, Penny KI, et al. The epidemiology of chronic pain in the community. *Lancet*. 1999;354:1248–1252.
- Frießem CH, Willweber-Strumpf A, Zenz MW. Chronic pain in primary care. German figures from 1991 and 2006. *BMC Public Health*. 2009;9:299.
- Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150:971–979.
- Watkins LR, Wiertelak EP, Goehler LE, et al. Neurocircuitry of illness-induced hyperalgesia. *Brain Res*. 1994;639:283–299.
- Apkarian AV, Baliki MN, Geha PY. Towards a theory of chronic pain. *Prog Neurobiol*. 2009;87:81–97.
- Jensen MP. Psychosocial approaches to pain management: an organizational framework. *Pain*. 2011;152:717–725.
- Loeser JD, Melzack R. Pain: an overview. *Lancet*. 1999;353:1607–1609.
- Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc*. 2003;78:1463–1470.
- Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357:266–281.
- Benson J, Wilson A, Stocks N, et al. Muscle pain as an indicator of vitamin D deficiency in an urban Australian Aboriginal population. *Med J Aust*. 2006;185:76–77.
- Lotfi A, Abdel-Nasser AM, Hamdy A, et al. Hypovitaminosis D in female patients with chronic low back pain. *Clin Rheumatol*. 2007;26:1895–1901.
- Atherton K, Berry DJ, Parsons T, et al. Vitamin D and chronic widespread pain in a white middle-aged British population: evidence from a cross-sectional population survey. *Ann Rheum Dis*. 2009;68:817–822.
- Mouyis M, Ostor AJ, Crisp AJ, et al. Hypovitaminosis D among rheumatology outpatients in clinical practice. *Rheumatology (Oxford)*. 2008;47:1348–1351.
- Heath KM, Elovic EP. Vitamin D deficiency: implications in the rehabilitation setting. *Am J Phys Med Rehabil*. 2006;85:916–923.
- Straube S, Andrew Moore R, Derry S, et al. Vitamin D and chronic pain. *Pain*. 2009;141:10–13.
- Lyrithis GP, Androulakis C, Magiasis B, et al. Effect of nandrolone decanoate and 1-alpha-hydroxy-calciferol on patients with vertebral osteoporotic collapse. A double-blind clinical trial. *Bone Miner*. 1994;27:209–217.
- Iwamoto J, Takeda T, Ichimura S, et al. Effects of cyclical etidronate with alfacalcidol on lumbar bone mineral density, bone resorption, and back pain in postmenopausal women with osteoporosis. *J Orthop Sci*. 2003;8:532–537.
- Gloth FM III, Lindsay JM, Zelesnick LB, et al. Can vitamin D deficiency produce an unusual pain syndrome? *Arch Intern Med*. 1991;151:1662–1664.
- Palmieri GM, Pitcock JA, Brown P, et al. Effect of calcitonin and vitamin D in osteoporosis. *Calcif Tissue Int*. 1989;45:137–141.
- Dottori L, D’Ottavio D, Brundisini B. Calcifediol and calcitonin in the therapy of rheumatoid arthritis. A short-term controlled study. *Minerva Med*. 1982;73:3033–3040.
- Warner AE, Arnsperger SA. Diffuse musculoskeletal pain is not associated with low vitamin D levels or improved by treatment with vitamin D. *J Clin Rheumatol*. 2008;14:12–16.
- Block SR. Vitamin D deficiency is not associated with non-specific musculoskeletal pain syndromes including fibromyalgia. *Mayo Clin Proc*. 2004;79:1585–1586; author reply 1586–1587.
- Wandless I, Jarvis S, Evans JG, et al. Vitamin D3 in osteoporosis. *Br Med J*. 1980;280:1320.
- Grove O, Halver B. Relief of osteoporotic backache with fluoride, calcium, and calciferol. *Acta Med Scand*. 1981;209:469–471.
- de Torrente de la Jara G, Pecoud A, Favrat B. Musculoskeletal pain in female asylum seekers and hypovitaminosis D3. *BMJ*. 2004;329:156–157.
- Lee P, Chen R. Vitamin D as an analgesic for patients with type 2 diabetes and neuropathic pain. *Arch Intern Med*. 2008;168:771–772.
- Chapman JR, Norvell DC, Hermsmeyer JT, et al. Evaluating common outcomes for measuring treatment success for chronic low back pain. *Spine*. 2011;36:S54–S68.
- Turk DC, Dworkin RH, Revicki D, et al. Identifying important outcome domains for chronic pain clinical trials: an IMMPACT survey of people with pain. *Pain*. 2008;137:276–285.
- Pilowsky I, Crettenden I, Townley M. Sleep disturbance in pain clinic patients. *Pain*. 1985;23:27–33.
- Smith MT, Perlis ML, Smith MS, et al. Sleep quality and presleep arousal in chronic pain. *J Behav Med*. 2000;23:1–13.
- McCarty DE. Resolution of hypersomnia following identification and treatment of vitamin d deficiency. *J Clin Sleep Med*. 2010;6:605–608.
- Manchikanti L, Singh V, Datta S, et al. Comprehensive review of epidemiology, scope, and impact of spinal pain. *Pain Physician*. 2009;12:E35–E70.
- McEoy G. *AHFS Drug Information 2007. Vitamin D Analogs General Statement*. Bethesda, MD: American Society Health-Systems Pharmacists; 2007.
- Jensen MP, Karoly P, O’Riordan EF, et al. The subjective experience of acute pain. An assessment of the utility of 10 indices. *Clin J Pain*. 1989;5:153–159.
- Kazis LE, Miller DR, Clark J, et al. Health-related quality of life in patients served by the Department of Veterans Affairs: results from the Veterans Health Study. *Arch Intern Med*. 1998;158:626–632.
- Kazis LE, Miller DR, Clark JA, et al. Improving the response choices on the veterans SF-36 health survey role functioning scales: results from the Veterans Health Study. *J Ambul Care Manage*. 2004;27:263–280.
- Kazis LE, Miller DR, Skinner KM, et al. Patient-reported measures of health: the Veterans Health Study. *J Ambul Care Manage*. 2004;27:70–83.
- Ware JEJ, Kosinski M, Keller SD. *SF-36 Physical and Mental Health Summary Scales: A User’s Manual*. Boston MA: Health Assessment Lab; 1994.
- Buyse DJ, Reynolds CF III, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28:193–213.
- Liang K-Y, Zeger SZ. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986;73:13–22.
- National Center for Veterans Analysis and Statistics. Veteran Population. 2011; Available at: http://www.va.gov/vetdata/Veteran_Population.asp. Accessed July 25, 2011.
- Callister P, Galtry J, Didham R. The risks and benefits of sun exposure: should skin colour or ethnicity be the main variable for communicating health promotion messages in New Zealand? *Ethn Health*. 2011;16:57–71.
- Nesby-O’Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988–1994. *Am J Clin Nutr*. 2002;76:187–192.
- Mygind A, Traulsen JM, Norgaard LS, et al. The ambiguity of ethnicity as risk factor of vitamin D deficiency—A case study of Danish vitamin D policy documents. *Health Policy*. 2011;102:56–63.
- Sakalli H, Arslan D, Yucler AE. The effect of oral and parenteral vitamin D supplementation in the elderly: a prospective, double-blinded, randomized, placebo-controlled study. *Rheumatol Int*. 2011 [Epub ahead of print].
- Stiefel F, Stagno D. Management of insomnia in patients with chronic pain conditions. *CNS Drugs*. 2004;18:285–296.