Evaluation of Vitamin D Supplementation in a Veteran Population

Emily Pherson, PharmD; Karen Korch-Black, PharmD, CGB; Melissa Tiedeman, PharmD, BCPS; and Amy Chung, PharmD, MS, BCPS

Study investigators reviewed charts of 185 patients on various vitamin D supplementation regimens, to identify current prescribing and monitoring patterns and find out whether vitamin D sufficiency was achieved.

Vitamin D deficiency is implicated in several different diseases, including cancer, cardiovascular disease, diabetes, mental illness, multiple sclerosis, osteoporosis, and many others.[1-4] Patients at risk for vitamin D deficiency include those who are aged ≥ 65 years, have darker skin, live in northern latitudes, have a history of osteoporosis or chronic kidney disease (CKD), or are taking medications that can affect vitamin D levels (eg, melphalan).[5] There is no consensus as to the definition of sufficient, insufficient, and deficient vitamin D levels. However, most experts define vitamin D deficiency as a 25-hydroxyvitamin D [25(OH)D] level of ≤ 20 ng/mL. Levels of 21 ng/mL to 29 ng/mL are considered insufficient, and levels ≥ 30 ng/mL are considered sufficient.[3] To prevent or improve some diseases associated with low vitamin D levels, higher 25(OH) D levels may be needed. One study found that 25(OH)D levels need to be 38 ng/mL to improve muscular performance and that levels of 52 ng/mL are needed to reduce the incidence of breast cancer.[1] Yet another study concluded that levels of 36 ng/mL to 48 ng/mL should be achieved to maintain "optimal health."[5]

Ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) are the 2 most common forms of vitamin D contained in supplements used to treat vitamin D deficiencies.[5] Generally, cholecalciferol is more effective in raising 25(OH)D levels than ergocalciferol.[1] The lowest effective treatment dose of vitamin D is 800 IU/d; however, no consensus exists on the ideal dosing regimen.[1] Official guidelines exist for the treatment of vitamin D deficiency/insufficiency in patients with CKD stages 3 and 4.[6] The recommended dosing for the prevention of bone fractures is 600 IU to 800 IU of vitamin D3 daily.[7]

A retrospective study evaluated several vitamin D regimens and found that ergocalciferol 50,000 IU 3 times weekly for 6 weeks corrected vitamin D deficiency in 95% of patients and insufficiency in 82% of patients. They also found that regardless of regimen, vitamin D sufficiency (≥ 30 ng/mL) was most frequently achieved when patients received ≥ 600,000 IU of a combination of vitamins D2 and D3 total over a mean of 60 days. Based on this finding, total dose of vitamin D, rather than the frequency of dosing, may be more predictive of achieving vitamin D sufficiency.[8] Dosing adjustments may be necessary in obese patients. Since vitamin D is a fat-soluble vitamin, patients with large amounts of body fat will require larger doses. Elderly patients have decreased vitamin D skin metabolism; therefore, this population may require increased doses as well.[1]

The Veterans Affairs Maryland Health Care System (VAMHCS) is a multifacility network of medical centers and clinics with a total of 754 beds and 7 outpatient clinics serving more than 50,000 patients throughout Maryland. At the VAMHCS, there has been a trend toward increased prescribing of vitamin D supplements. Currently, the VAMHCS, like many other institutions, does not have a protocol for vitamin D prescribing and monitoring. The Baltimore Veterans Affairs Medical Center (VAMC) is the acute medical and surgical care facility for the VAMHCS and offers a full range of inpatient, outpatient, and primary care services. This study aimed to determine the current practices regarding prescribing and monitoring of vitamin D supplementation at the Baltimore VAMC. To accomplish this, a retrospective study design was used to identify current prescribing and monitoring patterns for vitamin D supplementation. The study also evaluated whether patients receiving vitamin D supplementation achieved vitamin D sufficiency.

Ms. Pherson is a PGY2 pharmacotherapy resident at The Johns Hopkins Hospital in Baltimore, Maryland. **Ms. Tiedeman** is a clinical pharmacist at the Warrior Transition Clinic, Walter Reed National Military Medical Center, in Bethesda, Maryland. **Mrs. Chung** and **Mrs. Korch-Black** are clinical pharmacy specialists and Mrs. Korch-Black is also program director, PGY2 ambulatory care residency, at the VA Maryland Health Care System, in Baltimore, Maryland.

Table 1. Patient demographics	
Average age (± SD)	62 (13.9)
Race (%)	
Black	52
White	42
Other	7
Comorbid diseases (%)	
CKD	20
Osteoporosis	5
Previous CVA	11
PVD	8
CAD	21
Hyperparathyroidism	3

METHODS

The University of Maryland School of Medicine Institutional Review Board and VAMHCS Research and Development committee approved the study. Patients (aged > 18 years) were included in the study if they had an index prescription for ergocalciferol 50,000 IU, vitamin D (cholecalciferol) 400 IU, or vitamin D (cholecalciferol) 1,000 IU between November 1, 2008, and November 30, 2009. Patients meeting inclusion criteria were identified using the VAMHCS Computerized Patient Record System (CPRS), which contained pertinent laboratory, pharmacy, and administrative data. Exclusion criteria included those patients who were aged < 18 years, receiving hemodialysis, status postgastric bypass surgery, or taking cholestyramine, colestipol, or orlistat. Patients with a history of rickets, osteomalacia, celiac sprue, cystic fibrosis, or short-bowel syndrome were also excluded. Before beginning the study, the authors recognized that the total number of patients who met the inclusion criteria would be too large to successfully complete a chart review for each of them. Given the time allotted for data collection, it was determined that approximately 200 patient charts would be reviewed.

The following data were collected by performing an electronic chart review via CPRS:

- Age and race
- Comorbid diseases (CKD, osteoporosis, previous cerebral vascular accident [CVA], peripheral vascular disease [PVD], coronary artery disease [CAD], and hyperparathyroidism)
- Vitamin D regimen, total vitamin D dose
- Clinic from which the prescription originated
- Baseline 25(OH)D level, number of months until follow-up vitamin D level, follow-up vitamin D level
- Changes in vitamin D prescription in response to the follow-up vitamin D level

Levels for 25(OH)D were determined by Quest Diagnostics liquid chromatography and tandem mass spectrometry during the study period.

Descriptive statistics were compiled for demographic data, vitamin D dosing regimens, pertinent laboratory data (to evaluate both baseline level and frequency of monitoring), and the specific clinics from where the vitamin D prescription originated. Analyses were performed to determine the number of patients that achieved repletion (defined as a vitamin D level > 30 ng/mL), the number of patients who were prescribed a maintenance regimen, the supplementation regimen that was prescribed based on the baseline vitamin D level, and the duration of time from baseline vitamin D level to issuance of the vitamin D supplementation prescription. Further analysis was performed to determine what regimens and total doses were being prescribed by the individual clinics. As a quality measure, the amount of supplementation prescribed vs the amount that was dispensed was analyzed to identify discrepancies. To evaluate safety, any documentation of overdose (defined as patient failure to understand dosing instructions resulting in more frequent administration of vitamin D supplement than prescribed) was noted and further reviewed by the authors.

RESULTS

Between November 1, 2008, and November 30, 2009, 1,859 subjects with an index prescription for a vitamin D supplement were identified. To conduct this study in a limited period of time, subjects were randomized (using the online tool, Research Randomizer) for a population of 185.[9] A sample size of 185 (about 10% of the total population) was chosen, as it was close to the 200 charts the authors originally thought could be reviewed in the time allotted for data collection. A rolling inclusion method was used; therefore, if a subject met the exclusion criteria, the next subject was included until a total of 185 patients were obtained. Patient characteristics are outlined in Table 1.

The 185 patients received vitamin D supplement prescriptions originating from 17 unique provider areas within the Baltimore VAMC. The majority of the prescriptions (99/185) originated from primary care. There were a total of 35 different vitamin D repletion regimens prescribed to the 185 patients. The most commonly prescribed regimen was ergocalciferol 50,000 IU once weekly for 8 weeks. The average cumulative dose prescribed for vitamin D repletion was 678,320 IU. Of the 185 patients, 57.9% had a follow-up vitamin D level drawn. For those patients who had a follow-up level, time from the issue date of the supplement prescription to having the follow-up vitamin D level drawn averaged 30.5 weeks (SD ± 17.4). Vitamin D levels postsup-

plementation increased an average of 21.6 ng/mL from baseline, and repletion occurred in 53.6% of patients. The average total dose when repletion was achieved was 667,496 units (combination of vitamin D2 and D3), and the average total dose when repletion was not achieved was 485,242 units (combination of vitamin D2 and D3). Maintenance vitamin D regimens were prescribed for 54% of patients. These parameters were further examined by the individual provider area (Table 2).

When looking at the type of supplementation that was prescribed based on baseline vitamin D levels, 96% of patients with a baseline level of 3 ng/mL to 9 ng/mL, 87% of patients in the range of 10 ng/mL to 19 ng/mL, 54% of patients in the range of 20 ng/mL to 29 ng/mL, and 17% of patients with initial levels > 30 ng/mL received ergocalciferol in varying regimens (Table 3).

When analyzing pharmacy records, there were a total of 16/185 instances where the amount of ergocalciferol dispensed differed from the amount that was prescribed. This occurred most frequently in the primary care clinic (62.5%). There were instances of both over- and underdispensing, in the range of – 3 to + 4 capsules of the actual amount of ergocalciferol prescribed.

Of the 185 patients, there was 1 instance of vitamin D overdose. The patient was residing in a mental health unit at the time and taking part in a residential treatment program for substance abuse. The baseline vitamin D level was 22 ng/mL, and ergocalciferol 50,000 units once weekly for 8 weeks was prescribed. Upon medication review a nurse discovered that the patient was taking the ergocalciferol daily rather than weekly for a total of 300,000 units in 6 days (self-administration of medications was permitted on this unit). The patient was advised to stop taking ergocalciferol and was evaluated for vitamin D toxicity. The patient said he experienced no anorexia, nausea, vomiting, polyuria, polydipsia, weakness, nervousness, pruritis, or mental status changes, and the EKG was not significantly changed from baseline. A follow-up vitamin D level was drawn and found to be 60 ng/mL. The patient was later counseled on the correct administration of ergocalciferol and on the signs and symptoms of vitamin D toxicity. It was determined that this patient did not suffer any adverse effects from the overdose.

When analyzing pharmacy records, there were a total of 16/185 instances where the amount of ergocalciferol dispensed differed from the amount that was prescribed.

DISCUSSION

This study was able to describe the current prescribing and monitoring practices for vitamin D supplementation (both vitamin D2 and D3) at the Baltimore VAMC. Based on the results of the study, it was determined that achieving total vitamin D doses ≥ 600,000 IU over the repletion period was a key component to successful vitamin D repletion. It may also be prudent to ensure that timely follow-up 25(OH)D levels are obtained to facilitate proper vitamin D repletion.

Obtaining repeat 25(OH)D levels 3 months after therapy initiation is suggested to evaluate the effectiveness of the vitamin D supplementation for those being treated for vitamin D deficiency.[1] It is recommended that for patients being supplemented with ergocalciferol, this follow-up level be drawn at the conclusion of supplementation with ergocalciferol, prior to beginning maintenance therapy. In this study it took an average of 7 months to collect a follow-up vitamin D level. It should be noted that obtaining a follow-up level is dependent on not only the provider ordering the level, but also the patient returning to the Baltimore VAMC for the blood draw. However, the VA system does make it easier for patients to obtain laboratory values, as they have various clinic locations where patients can get their laboratory work done. It may be beneficial for providers to make their first attempt to notify patients that they are due for their vitamin D level a few weeks prior to the 3-month mark, to allow them adequate time to return to have the level drawn.

This study confirmed the findings in the Pepper and colleagues study that vitamin D sufficiency (≥ 30 ng/mL) was most frequently achieved when patients received ≥ 600,000 IU of vitamin D (combinations of vitamin D2 and D3) in total throughout the supplementation period.[8] The most frequently prescribed regimen in this study, ergocalciferol once weekly for 8 weeks, did not reach this 600,000 IU total. Other regimens that were less frequently prescribed but reached 600,000 IU throughout the course of therapy were more successful at repletion. Given the infrequency of prescribing a total of 600,000 IU, educating prescribers that this should be the total

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Table 2. Breakdown of specific parameters by prescribing clinic[a]

Clinic	Patients receiving vitamin D supplement Rxs (N)	Average total dose (units)	Follow-up vitamin D levels (%)	Time to follow-up vitamin D level in weeks (± SD)	Increase in vitamin D level (ng/mL)	Repletion achieved (%)	Maintenance regimens prescribed (%)	Follow-up for which a response was noted by provider[b]	Time to supplement Rx date from time baseline vitamin D was drawn (weeks)
Primary care	99	609,823	44.4	25.4 (± 12.2)	17.5	50.0	48.5	81.8	25.0
Endocrinology	17	666,231	64.7	24.0 (± 13.3)	21.3	55.6	64.7	81.8	22.3
Inpatient	14	323,883	42.9	18.0 (± 20.1)	25.2	81.4	28.6	62.9	21.4
Diabetes	11	792,620	63.6	16.7 (± 8.7)	18.1	42.9	54.5	71.4	73.0
Nephrology	11	613,636	54.5	20.3 (± 5.4)	11.3	33.3	18.1	50.0	33.3
Mental health	7	284,467	71.4	16.8 (± 10.5)	12.0	40.0	42.9	100.0	12.1
Women's health	6	463,067	66.7	15.8 (± 2.5)	30.5	75.0	66.7	75.0	18.3
Early renal insufficiency	5	750,000	80.0	28.5 (± 18.8)	31.3	100.0	20.0	0.0	15.2
Pain	4	1,350,000	50.0	73.0 (± 72.1)	8.5	0.0	50.0	100.0	20.75
Arthritis	3	600,000	0.0	-	-	-	66.7	-	43.6
Infectious disease	2	1,300,000	100.0	34.0 (± 38.0)	47.5	50.0	50.0	100.0	9.0
Oncology	2	400,000	50.0	50.4 (± N/A)[c]	21.0	100.0	100.0	100.0	5.0
Gastroenterology	1	900,000	100.0	14.9 (± N/A)[c]	10.0	100.0	0.0	0.0	17.0
Hepatitis	1	1,200,000	100.0	39.0 (± N/A)[c]	13.0	0.0	100.0	100.0	18.0
Medical preoperative	1	700,000	0.0	-	-	-	100.0	-	41.0
Neurology	1	200,000	0.0	-	-	-	100.0	-	29.0
Baltimore VAMC	185	678,320	57.9	30.5 (± 17.4)	21.6	53.6	54	72.9	23.8

[a]The averages for the entire Baltimore VAMC are listed in addition to the results from the individual clinics.
[b]Response: Note in patients chart that indicated provider action on follow-up vitamin D level.
[c]N/A indicates that only 1 follow-up level was obtained in respective clinic; therefore, SD was unable to be calculated.
Rx = prescription; SD = standard deviation.

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Table 3. Baseline vitamin D vs choice of supplementation regimen

Baseline vitamin D level	3-9 ng/mL (%)	10-19 ng/mL (%)	20-29 ng/mL (%)	> 30 ng/mL (%)	Started supplementation without baseline level (%)	Totals
Total patients	25 (13.5)	88 (47.6)	56 (30.3)	6 (3.2)	10 (5.9)	185
Ergocalciferol	24 (96)	78 (88.6)	30 (53.6)	1 (16.7)	3 (36.4)	136
1,000 units vitamin D	0 (0)	6 (6.8)	15 (26.8)	2 (33.3)	3 (27.2)	26
400 units vitamin D	1 (4)	4 (4.5)	11 (19.6)	3 (50.0)	4 (36.4)	23

amount of vitamin D supplementation they should be aiming for is extremely important. In this study, there did not seem to be any correlation between baseline vitamin D level and type of vitamin D supplementation regimen prescribed. Developing specific regimens that correlate to baseline levels may be advantageous in making sure patients reach repletion. This is definitely a strong education point for prescribers.

The fact that there was some discrepancy between the amount prescribed and the amount dispensed warrants further investigation. It is possible that there may be an error on the dispensing end or prescribers are writing for a quantity that is a few extra doses beyond the prescribed regimen. In this study, the amount of extra capsules dispensed was not likely to cause toxicity if patients took the extra capsules; however, this possibility certainly exists if patients are nonadherent to the regimen as prescribed.

While there are many benefits to maintaining adequate levels of vitamin D, vitamin D supplementation should be used with caution in patients with hypercalcemia, primary hyperparathyroidism, or a history of renal stones.[5] Patients with diabetes mellitus or hypertension (HTN) may experience hypoglycemia or hypotension when treated with physiologic (5,000 IU/d for adults) doses of vitamin D. If either occurs, the doses of the diabetes or HTN medication should be lowered instead of lowering the dose of vitamin D supplementation.[1] Drugs that impair fat absorption such as cholestyramine, colestipol, and orlistat may also impair vitamin D absorption.[10] Patients on these medications were excluded from the study.

The National Academy of Sciences defines the safe upper limit for vitamin D as 2,000 IU/d; however, newer studies have reported that upper limits up to 10,000 IU/d are safe and necessary in some patients to achieve sufficient vitamin D levels.[1,10] Levels of 25(OH) D exceeding 150 ng/mL are generally considered toxic and may be associated with hypercalcemia.[5] For hypercalcemia to occur, patients would need to take ≥ 10,000 IU/d for several months and perhaps even years.[1] In this study, 1 incidence of vitamin D overdose was identified with a subsequent follow-up level of 60 ng/mL. The patient did not experience any symptoms of vitamin D toxicity, which is consistent with current literature findings that levels may need to exceed 150 ng/mL to cause symptomatic toxicity.

Since the conclusion of this study, clinical practice guidelines on the evaluation, treatment, and prevention of vitamin D deficiency were developed by The Endocrine Society and published in July 2011.[11] The definitions proposed for vitamin D deficiency, insufficiency, and sufficiency are identical to those proposed in this article. For treatment of vitamin D deficient adults, the guidelines suggest 50,000 IU of vitamin D2 or vitamin D3 once a week for 8 weeks, or its equivalent of 6,000 IU of vitamin D2 or vitamin D3 daily, to achieve a blood level of 25(OH)D above 30 ng/mL, followed by maintenance therapy of 1,500 to 2,000 IU/d. This recommendation is in line with the most frequently prescribed regimen in this study. The guidelines include alternative treatment regimens for nursing home residents of 50,000 IU of vitamin D2 3 times a week for 1 month or 100,000 IU of vitamin D every 4 months. The former regimen is in line with the total of 600,000 IU/repletion period, which was associated with successful repletion in this study. For obese patients or those with malabsorption syndromes, the guidelines recommend vitamin D dosing 2 to 3 times higher than in adults without these conditions. They recommend vitamin D supplementation for fall prevention but do not recommend supplementation (beyond regular daily requirements of 600 to 800 IU/d for patients aged > 50 years) for preventing cardiovascular disease,

death, or improving quality of life.[11] The recommendation regarding cardiovascular disease is in line with a systemic review and meta-analysis published in July 2011, which did not demonstrate a statistically significant reduction in mortality and cardiovascular risk associated with vitamin D.[12] The guidelines did not make any recommendations for obtaining follow-up vitamin D levels.

CONCLUSION

This review found a large variation between initial vitamin D replenishment regimens, occurrence of follow-up, ability to reach therapeutic vitamin D levels, and conversion to maintenance vitamin D regimens postreplenishment within a single medical center. Given this wide variation, providers and patients may benefit from further education regarding optimal vitamin D repletion therapy and appropriate monitoring. Providers can be educated about the optimal dosing and monitoring parameters described in this study. Patients can become their own advocates by being educated about the importance of vitamin D supplementation and being given adequate reminders about when to get follow-up vitamin D levels. Another area for future research includes duration of time patients remain in repletion after the vitamin D supplementation regimen is completed.

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