Journal of Pharmacy Practice
1-5
© The Author(s) 2014
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/0897190014544822
jpp.sagepub.com
SAGE

A Retrospective Evaluation of Response to Vitamin D Supplementation in Obese Versus Nonobese Patients

Ginelle A. Bryant, PharmD, BCPS[1], Carrie Foust Koenigsfeld, PharmD, FAPhA[1], Nicholas P. Lehman, PharmD, BCACP[1], Hayden L. Smith, PhD[2,3], Craig D. Logemann, PharmD, BCACP, CDE[4], and Kirk T. Phillips, PhD[5]

Abstract

Objective: To evaluate the impact of body mass index (BMI) on vitamin D status following ergocalciferol therapy. *Methods:* A retrospective evaluation of patients aged 18 years and older with a baseline serum 25(OH)D < 30 ng/mL who received prescription ergocalciferol 50 000 IU at any dose between July 2009 and November 2011 was conducted. Patients were included if pre- and posttreatment 25(OH)D levels were available within 3 months of therapy. *Results:* Two hundred and thirteen patients were included in the study with 52% having a BMI $\geq$30 kg/m^2. Thirty-eight different ergocalciferol regimens were prescribed, and the majority of patients (66.2%) received a regimen consisting of 50 000 IU once weekly for variable durations. Mean 25(OH)D levels increased from 18.8 $\pm$ 6.6 ng/mL at baseline to 35.0 $\pm$ 13.8 ng/mL with 61.0% (n = 130) of patients having attained vitamin D sufficiency, 25(OH)D $\geq$ 30 ng/mL, with their prescribed ergocalciferol regimen. Obese patients with a BMI $\geq$30 were less likely to attain vitamin D sufficiency following replacement than patients with a BMI <30 kg/m^2 (52% vs 71%; $P = .0161$). *Conclusion:* Our study demonstrated an overall moderate response rate to replacement therapy with ergocalciferol and considerable variability in vitamin D replacement strategies initiated by primary care providers. Based on our findings, elevated BMI $\geq$30 kg/m^2 may impact the likelihood of attaining vitamin D sufficiency with ergocalciferol.

Keywords

vitamin D, ergocalciferol, obesity

Background

Evidence has suggested a relationship between vitamin D insufficiency and obesity, with studies demonstrating the presence of low serum 25-hydroxyvitamin D, 25(OH)D, levels in both obese children and obese adults.[1-6] Wortsman et al postulated that this relationship is due in part to the sequestration of fat soluble vitamin D in the thicker body fat compartments of obese patients.[1] Another proposed mechanism is that increased serum parathyroid hormone levels and the active form of vitamin D (1,25-dihydroxyvitamin D) seen in obese versus nonobese individuals results in an enhanced negative feedback mechanism on the hepatic production of 25(OH)D.[5-6] The Institute of Medicine, Food and Nutrition Board recommends Dietary Reference Intakes for vitamin D of 600 International Units (IU; age 1-70 years).[7] Some experts suggest that obese patients should be treated with at least twice as much vitamin D as a normal weight individual in order to maintain a normal vitamin D status.[1]

Currently, several interventional studies have characterized an inverse relationship between obesity and vitamin D status.[1,2-6,8] Information regarding appropriate replacement doses of vitamin D to adequately raise 25(OH)D levels in adults is lacking, and even more limited information regarding the impact of weight on serum levels is available. The goal of the present study was to determine whether vitamin D levels following replacement doses of ergocalciferol differed between obese and nonobese patients.

[1] Department of Clinical Sciences, Drake University College of Pharmacy and Health Sciences, Des Moines, IA, USA
[2] Medical Education, Iowa Methodist Medical Center, Des Moines, IA, USA
[3] Internal Medicine, Carver College of Medicine, University of Iowa, Iowa City, IA, USA
[4] UnityPoint Health, Des Moines, IA, USA
[5] Strategic Analytics Department, UnityPoint Health, Des Moines, IA, USA

Corresponding Author:
Ginelle A. Bryant, Department of Clinical Sciences, Drake University College of Pharmacy and Health Sciences, 2507 University Avenue Des Moines, IA 50311, USA.
Email: ginelle.bryant@drake.edu

Downloaded from jpp.sagepub.com at PENNSYLVANIA STATE UNIV on May 12, 2016

Methods

A retrospective cohort design was used to evaluate the effectiveness of ergocalciferol (vitamin D2) treatment for vitamin D deficiency in a community setting. The study was submitted and approved by the local health system's institutional review board. Study patients were identified from 6 outpatient medical clinics within a health system, including 4 internal medicine clinics and 2 family medicine clinics, located in a medium-sized Midwestern city. Vitamin D deficiency was defined as a serum 25(OH)D concentration <30 ng/mL. Potential study patients were identified using electronic medical records and were included in the study if they were at least 18 years of age, had a baseline vitamin D level < 30 ng/mL, received vitamin D therapy with prescription strength ergocalciferol (50 000 IU) at any frequency during study period of July 2009 through November 2011, and if pre- and posttreatment 25(OH)D levels were available within 3 months of having completed ergocalciferol therapy. Patients were excluded if they had significant renal dysfunction (estimated glomerular filtration rate [GFR] less than 30 mL/min) or the presence or history of malabsorption disorders (ie, Celiac disease, Crohn's disease, ulcerative colitis, Whipple's disease, or cystic fibrosis). Dispensing pharmacies were contacted via fax to confirm whether patients picked up their prescribed vitamin D product and any prescribed refills. Patients were excluded if the dispensing pharmacy indicated that patient did not pick up any portion of their ergocalciferol prescription. If the dispensing pharmacy did not reply with prescription fill information, then these patients were included in the sample.

The primary study outcome was to evaluate the impact of BMI on vitamin D status following prescription ergocalciferol therapy. BMI was calculated using kg/m^2, and patients were dichotomized based on a BMI value of either <30 or ≥30 kg/m^2. Data on other pertinent clinical covariates were collected to assess for potential confounders. These clinical covariates included gender, age, season in which follow-up vitamin D levels were measured, and relative timing of therapy completion and measurement of follow-up vitamin D levels. The secondary study outcome was to define the types of vitamin D regimens prescribed in the primary care setting, including the dose and duration of therapy.

Data were extracted from clinic records and recorded in a study database for initial evaluation. Descriptive statistics were used to evaluate completeness and accuracy of coded values for study variables. Comparative analyses were conducted examining vitamin D deficiency status after therapy based on study variables using Fisher's exact test and Student's *t* test.

Multiple logistic regression was performed to examine variables associated with serum vitamin D deficiency after the ergocalciferol repletion regimen. Deficiency status was used as the dependent binary variable (ie, patients who did not attain vitamin D sufficiency following therapy with a 25(OH)D level ≥30 ng/mL versus patients who did attain vitamin D sufficiency). Candidate independent variables were considered for inclusion based on comparative statistics and clinical relevance. A final best fit parsimonious model was constructed based on 0.05 level of significance and clinical relevance. Model fit was examined with Hosmer-Lemeshow (H-L) test and discrimination with the c-statistic. Final model covariates were presented with beta coefficient (β), standard error (SE), and *P* value. Adjusted odds ratios (AORs) for deficiency were calculated with 95% confidence intervals (CI). Statistical tests were 2 tailed and based on a 0.05 level of significance. Statistical procedures were conducted with SAS 9.3 (SAS Institute, Cary, North Carolina).

Table 1. Baseline Characteristics for Discrete Variables.[a]

Characteristic	N	%
Female	172	80.70
Body mass index, kg/m^2		
<30	103	48.40
≥30	110	51.60
Season at postmeasurement		
Spring–summer	115	54.00
Fall–winter	98	46.00
Time between completing therapy and follow-up vitamin D level		
<1 mo	129	60.60
1-3 mo	84	39.40
Total weekly dose of vitamin D, IU		
50 000	141	66.20
100 000	55	25.80
150 000	10	4.70
12 500[b]	1	0.50
250 000	1	0.50
Other regimen	5	2.30
Characteristic	N	Mean
Age, years	213	59.9
Weight, pounds	213	186.9
BMI, kg/m^2	213	31
Baseline vitamin d level, ng/mL	213	18.8
Posttherapy vitamin D level, ng/mL	213	35
Change in vitamin D level, ng/mL	213	16.6
Duration of ergocalciferol therapy, weeks	213	9.4
Total weekly dose vitamin D, IU	208	68 810

Abbreviations: BMI, body mass index; mo, month.
[a]n = 213.
[b]Regimen used was ergocalciferol 50 000 IU once monthly.

Results

A total of 1701 patients were identified as having two 25(OH)D levels drawn during study period of July 2009 through November 2011 and screened for inclusion. Of those patients, 213 patients were included in the analysis. The most common reasons for exclusion were not being treated with prescription strength ergocalciferol following a low 25(OH)D level (n = 989) or not having a follow-up serum 25(OH)D level within 3 months following therapy (n = 404). Baseline characteristics for the study population are shown in Table 1. A similar percentage of patients were obese with a BMI ≥30 kg/m^2 versus nonobese with a BMI <30 kg/m^2 (obese 51.6% vs 48.4% nonobese). Thirty-eight different ergocalciferol regimens were

Downloaded from jpp.sagepub.com at PENNSYLVANIA STATE UNIV on May 12, 2016

Table 2. Specific Ergocalciferol Regimens Prescribed.[a]

Ergocalciferol regimen	No. of patients
50 000 IU once weekly × 8 weeks	67
50 000 IU once weekly × 12 weeks	37
50 000 IU twice weekly × 34 weeks	35
50 000 IU once weekly × 6 weeks	14
50 000 IU twice weekly × 10 weeks	6
50 000 IU twice weekly × 12 weeks	5
50 000 IU once weekly × 4 weeks	4
50 000 IU once weekly × 13 weeks	4
50 000 IU twice weekly × 4 weeks	4
Other regimens[b]	37

[a]n = 213.
[b]Regimens taken by 3 or fewer patients.

prescribed in the 213 patients (Table 2). The majority of patients (66.2%) were prescribed an ergocalciferol regimen consisting of 50 000 IU once weekly for variable durations (Table 1).

Vitamin D prescription history was obtained for 124 (58%) patients. Of these patients, 96 patients were confirmed to have received their full prescribed dose from the pharmacy, including any refills (45% of the total population included in the study). For those patients not receiving the full course of therapy (n = 28), 12 patients were noted to have received a portion of their prescribed dose. In the remaining patients (n = 16), no prescription history was provided by the dispensing pharmacy.

Mean 25(OH)D levels at baseline were 18.8 ± 6.6 ng/mL. After receiving therapy with ergocalciferol, the mean serum 25(OH)D level at follow-up was 35.0 ± 13.8 ng/mL, with a mean prescribed weekly ergocalciferol dose of 68 810 IU given over an average of 9.4 weeks. Following ergocalciferol therapy, 61.0% (n = 130) of patients attained sufficiency (ie, had a 25(OH)D concentration ≥ 30 ng/mL) with their prescribed ergocalciferol regimen.

Comparative analyses for study variables based on posttherapy 25(OH)D deficiency status are presented in Table 3. Patients did not differ on sex, age, GFR, and seasonality of final 25(OH)D measurement ($P > .05$). Patients, based on whether they attained vitamin D sufficiency or not, did differ based on weight, BMI, 25(OH)D level at baseline, changes in 25(OH)D levels from pre- to posttherapy, timing of posttherapy 25(OH)D measurement, and weekly/cumulative prescribed ergocalciferol dosages ($P < .05$).

The multiple logistic model for the prediction of 25(OH)D deficiency had good fit (H-L: 0.59) and discrimination (c-statistic: 0.80). Model covariates significantly associated with a 25(OH)D deficiency included measurement of final serum level at greater than 1 month after therapy was completed (β: 1.6825, SE: 0.3392; $P < .0001$) and BMI value equal to or greater than 30 m/kg^2 (β: 0.8152, SE: 0.3389; $P = .0161$), with the model controlling for baseline serum vitamin D level (β: −0.0975, SE: 0.0263; p = 0.0002) and cumulative ergocalciferol prescribed doses (β: −1.04E-6, SE: 5.69E-7; p = 0.0675). AORs for significant categorical variables include a 5.4 (95% CI 2.8-10.5) times greater odds for 25(OH)D deficiency if postmeasurement was taken 30 days or more after therapy and a 2.3 (95% CI 1.2-4.4) times greater odds of deficiency in patients with a BMI greater or equal to 30 m/kg^2.

Discussion

In the present study, a potential relationship between response to vitamin D therapy as measured by serum 25(OH)D levels and BMI was observed. Obese patients with a BMI ≥30 kg/m^2 were less likely to attain vitamin D sufficiency following replacement than patients with a BMI <30 kg/m^2. In fact, 64% of patients who did not attain vitamin D sufficiency were obese.

Similarly, in a previous trial, Vande Griend et al found that patients with a BMI of ≥30 kg/m^2 were less likely to attain sufficiency than those with a BMI <30 kg/m^2 (odds ratio 0.44, 95% CI 0.30-0.63).[9] Furthermore, those who were not able to attain vitamin D sufficiency were 2.5 times more likely to have been obese than those who attained vitamin D sufficiency ($P < .0001$). Of the total patients, 33% (n = 1446) included in the analysis were obese with a BMI ≥30 kg/m^2 and 25(OH)D levels only increased from 16.7 ng/mL at baseline to 18.3 ng/mL at follow-up in the nonattainment group. Because of the small increase in serum 25(OH)D levels following replacement, the authors attributed the lack of vitamin D sufficiency attained in these patients to nonadherence versus differences in weight alone.[9] In our study, baseline vitamin D levels increased from 16.1 ng/mL to 23.7 ng/mL in the nonattainment group, thus a more substantial increase in vitamin D levels following supplementation was observed. This suggests that the difference in attainment rates seen in obese versus nonobese patients may be less likely due to nonadherence in our study. Although we attempted to collect adherence information through pharmacy data, a limited number of pharmacies responded to the request for information on whether patients picked up their initial fill and subsequent refills. Thus, it is possible that nonadherence may have impacted the results of our study as well.

Additionally, vitamin D levels were significantly lower in the nonattainment group at baseline compared to the group that attained vitamin D sufficiency (16.1 ng/mL vs 20.4 ng/mL, $P < .001$). As noted previously, several studies have indicated that obese patients are more prone to vitamin D deficiency,[1-6] and therefore, it is not unexpected that obese patients might have a lower baseline vitamin D level. It is possible that lower baseline vitamin D levels might explain the reason for a lower attainment rate seen in this group; however, if this is the case, it is unlikely that this phenomenon could be avoided, given that obese patients have been demonstrated to have lower serum vitamin D levels.

In addition, previous studies have shown the potential need for increased doses of vitamin D in the obese population. In a small study of 17 hospitalized inpatients, Lee et al found a lower response to a 10 000 unit/d dose of vitamin D for 1 week in those with a BMI >25 kg/m^2 when compared to nonobese

Downloaded from jpp.sagepub.com at PENNSYLVANIA STATE UNIV on May 12, 2016

Table 3. Statistical Comparisons of Patients Based on Posttherapy 25(OH)D Deficiency Status.[a,b]

Variable	Patients who attained vitamin D sufficiency (n = 130)	Patients who did not attain vitamin D sufficiency (n = 83)	*P* value
Female	102 (78%)	70 (84%)	.3732
Age, years	61.2 [12.9]	57.8 [13.6]	.0680
Weight, pounds	180.9 [45.5]	196.2 [45.9]	.0180
Body mass index, kg/m^2			.0050
<30	73 (56%)	30 (36%)	
≥30	57 (44%)	53 (64%)	
Vitamin D level baseline, ng/mL	20.4 [6.0]	16.1 [6.7]	<.0001
Change in vitamin D level, ng/mL	22.3 [14.4]	7.6 [5.6]	<.0001
Season at Postmeasurement			
Spring–summer	67 [52%]	48 [58%]	.3997
Fall–winter	63 [48%]	35 [42%]	
Time between completing therapy and follow-up vitamin D level			<.0001
<1 month	99 (76%)	30 (36%)	
1-3 months	31 (24%)	50 (64%)	
Mean weekly dose of ergocalciferol, IU[c]			.0223
12 500	1 (1%)	0 (0%)	
18 750	0 (0%)	1 (1%)	
50 000	80 (62%)	63 (76%)	
92 857	0 (0%)	1 (1%)	
100 000	41 (32%)	15 (18%)	
150 000	8 (6%)	2 (2%)	
250 000	0 (0%)	1 (1%)	
Mean cumulative doses, IU	664 615 [435 020]	557 229 [290 828]	.0320

[a]n = 213.
[b]Counts with percentages are given in parentheses and means with standard deviations are given in brackets.
[c]Mean weekly dose calculated based on prescribed dose, including any loading doses and duration.

patients.[10] Although the study was only conducted over 1 week and with a set dose, a similar result was seen in the current study over time despite multiple different dosing regimens being prescribed.

In a study by Blum et al, it was found that change in 25(OH)D was negatively associated with obesity.[11] For every 5 kg/m^2 of BMI at baseline, the change in 25(OH)D level at 1 year was approximately 4 ng/mL lower. In general, this means heavier patients require higher doses of vitamin D supplementation to achieve adequate vitamin D repletion. However, this study used a standardized dose of 700 IU of vitamin D versus placebo. Our results show a much higher average dose for all patients, with all 213 patients taking doses of vitamin D 12 500 IU or higher weekly. Blum's theory that heavier patients will require higher doses is well founded, with the dose needed to attain sufficiency still uncertain. Our findings show 76% of the patients found deficient posttherapy were taking a standardized dose of 50 000 IU. This calls into question whether the dose requires continued titration, a longer treatment interval, or if there is a threshold to surpass sequestration of lipid soluble vitamin D in the thicker body fat of an obese patient.[1]

Overall, 61% of patients in this study attained vitamin D sufficiency with their prescribed vitamin D regimen, with the most common regimen being 50 000 IU weekly (68% all patients). This is similar to the attainment rate seen by Vande Griend and colleagues in which 56% of patients attained vitamin D sufficiency and 64% of patients were on this same prescribed regimen of 50 000 IU weekly.[9] This is a moderate response rate, and the large number of prescribed regimens used in both of these studies seems to suggest that there is an overall lack of consensus on the appropriate regimen needed for vitamin D replacement. Additionally, in our study, it was noted that when 25(OH)D levels were measured more than 1 month after having completed therapy, these patients were more likely to be in the nonattainment group following therapy when compared to patients who had a level checked less than 1 month following replacement. This demonstrates the importance of timely follow-up of serum levels and the subsequent initiation of maintenance therapy following vitamin D replacement. We did not collect information on maintenance therapy following vitamin D replacement, and since this is typically over the counter, it may not be as clearly documented in the electronic medical record. Thus, it is unclear whether this observed difference was due to a lack of maintenance therapy following replacement.

Furthermore, patients who attained adequate vitamin D levels also received higher doses, with a higher percentage of patients in the attainment group having received a weekly dose of >100 000 IU compared to those in the nonattainment group (38% vs 21%, respectively). Therefore, the difference in patient response seen in the obese versus nonobese cannot be attributed to obesity alone.

Downloaded from jpp.sagepub.com at PENNSYLVANIA STATE UNIV on May 12, 2016

Strengths of the current study include assessing the use of vitamin D as prescribed in outpatient primary care clinics, reflecting real-world use of prescription strength ergocalciferol. The results of our study add to the evidence that obese patients may have more difficulty attaining therapeutic vitamin D levels and that higher doses of vitamin D may need to be prescribed. Our study also documented the season in which a follow-up vitamin D level was drawn to attempt to control for vitamin D exposure from the environment. We were able to show the time of year had no effect on a patient's ability to attain sufficient vitamin D levels.

There are some study limitations with our study that should be noted. First, the described study was observational in design with a relatively small study sample. As noted, while we attempted to collect data on adherence, we were only able to confirm pharmacy fill information in 58% of the study population, with 45% of pharmacies reportedly having dispensed the full prescribed ergocalciferol dose. We are unable to determine whether the patients who picked up their prescription from the pharmacy actually took their medication, and we cannot account for the remaining 42% of patients in which prescription history was not obtained. Although this is indeed a limitation of the study, nonadherence is likely a realistic barrier to treatment with any medication, and given that patients with vitamin D sufficiency are not typically symptomatic, it is a likely issue in any clinical practice setting. Another limitation of the study was the variability in doses and timing of serum tests, particularly on follow-up. Additionally, we were unable to collect data on some additional factors impacting vitamin D status, including over-the-counter vitamin D use and patient race, as these data are often not reported in the electronic medical record. Future research with prospective interventions regarding specific vitamin D doses needed to attain therapeutic levels in obese patients would provide further knowledge regarding supplementation.

Conclusion

There is a lack of consensus on how to adequately replace patients who are vitamin D deficient. Our study demonstrated an overall moderate response rate to replacement supplementation and highlights the considerable variability in vitamin D replacement strategies initiated by primary care providers. Several potential factors can impact the likelihood of attaining vitamin D sufficiency with replacement supplementation, and in our evaluation, the primary factors included baseline vitamin D level, cumulative vitamin D replacement dose, timing of postreplacement vitamin D level, and elevated BMI $\geq$30 kg/m^2.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Wortsman J, Matsuoka LY, Chen TC, et al. Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr*. 2000;72(3):690-693.
2. Rajakumar K, Fernstrom JD, Holick MF, et al. Vitamin D status and response to vitamin D_3 in obese vs. non-obese African-American children. *Obesity*. 2008;16(1):90-95.
3. Mark S, Lambert M, Delvin E, et al. Higher vitamin D intake is needed to achieve serum 25(OH)D levels greater than 50 nmol/l in Québec youth at high risk of obesity. *Eur J Clin Nutr*. [serial online]. 2011;65(4):486-492.
4. Dong Y, Stallmann-Jorgensen IS, Pollock NK, et al. A 16-week randomized clinical trial of 2000 International Units daily vitamin D_3 supplementation in black youth; 25-hydroxyvitamin D, adiposity, and arterial stiffness. *J Clin Endocrinol Metab*. 2010;95(10):4584-4591.
5. Bell NH, Epstein S, Greene A, et al. Evidence for alteration of the vitamin D-endocrine system in obese subjects. *J Clin Invest*. 1985;76(1):370-373.
6. Liel Y, Ulmer E, Shary J, et al. Low circulating vitamin D in obesity. *Calcif Tissue Int*. 1988;43(4):199-201.
7. Institute of Medicine, Food and Nutrition Board. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academy Press; 2010.
8. Elizondo-Montemayor L, Ugalde-Casas PA, Serrano-González M, et al. Serum 25-hydroxyvitamin D concentration, life factors and obesity in Mexican children. *Obesity*. 2010;18(9):1805-1811.
9. Vande Griend JP, McQueen RB, Linnebur SA, et al. Prescription ergocalciferol dosing for vitamin D repletion: a retrospective evaluation. *Pharmacotherapy*. 2012;32(2):135-141.
10. Lee P, Greenfield JR, Seibel MJ, et al. Adequacy of vitamin D replacement in severe deficiency is dependent on body mass index. *Am J Med*. 2009;122(11):1056-1060.
11. Blum M, Dallal GE, Dawson-Hughes B. Body size and serum 25 hydroxy vitamin D response to oral supplements in healthy older adults. *J Am Coll Nutr*. 2008;27(2):274-279.

Downloaded from jpp.sagepub.com at PENNSYLVANIA STATE UNIV on May 12, 2016