ORIGINAL RESEARCH

A Predictive Equation to Guide Vitamin D Replacement Dose in Patients

Gurmukh Singh, MD, PhD, MBA, and Aaron J. Bonham, MS

Background: **Vitamin D is essential for bone health and probably the health of most nonskeletal tissues. Vitamin D deficiency is widespread, and recommended doses are usually inadequate to maintain healthy levels. We conducted a retrospective observational study to determine whether the recommended doses of vitamin D are adequate to correct deficiency and maintain normal levels in a population seeking health care. We also sought to develop a predictive equation for replacement doses of vitamin D.**

Methods: **We reviewed the response to vitamin D supplementation in 1327 patients and 3885 episodes of vitamin D replacement and attempted to discern factors affecting the response to vitamin D replacement by conducting multiple regression analyses.**

Results: **For the whole population, average daily dose resulting in any increase in serum 25-hydroxyvitamin D level was 4707 IU/day; corresponding values for ambulatory and nursing home patients were 4229 and 6103 IU/day, respectively. Significant factors affecting the change in serum concentrations of 25-hydroxyvitamin D, in addition to the dose administered, are (1) starting serum concentration of 25-hydroxyvitamin D, (2) body mass index (BMI), (3) age, and (f) serum albumin concentration. The following equation predicts the dose of vitamin D needed (in international units per day) to affect a given change in serum concentrations of 25-hydroxyvitamin D: Dose = [(8.52 − Desired change in serum 25-hydroxyvitamin D level) + (0.074 × Age) – (0.20 × BMI) + (1.74 × Albumin concentration) – (0.62 × Starting serum 25-hydroxyvitamin D concentration)]/(−0.002). Analysis of the dose responses among 3 racial groups—white, black, and others—did not reveal clinically meaningful differences between the races. The main limitation of the study is its retrospective observational nature; however, that is also its strength in that we assessed the circumstances seen in usual health care setting.**

Conclusions: **The recommended daily allowance for vitamin D is grossly inadequate for correcting low serum concentrations of 25-hydroxyvitamin D in many adult patients. About 5000 IU vitamin D3/day is usually needed to correct deficiency, and the maintenance dose should be ≥2000 IU/day. The required dose may be calculated from the predictive equations specific for ambulatory and nursing home patients. (J Am Board Fam Med 2014;27:495–509.)**

Keywords: **Ambulatory Care, Community Medicine, Drug Dosage Calculations, Laboratories, Nursing Homes, Osteoporosis, Primary Health Care, Vitamin D**

The optimum serum concentration of 25-hydroxyvitamin D and what constitutes vitamin D deficiency is controversial. Serum concentrations of 25-hydroxyvitamin D <10 ng/mL are generally accepted to be deficient; however, 16 to 30 ng/mL or even higher is considered by different organizations and investigators to be the optimum concentration.[1–9] It has been suggested that levels of 40 to 60 ng/mL are ideal and that levels up to 100 ng/mL are safe.[5,7–9] If we accept that serum concentration of 30 ng/mL is optimal for 25-hydroxyvitamin D, then inadequacy of vitamin D may be the commonest nutritional deficiency in the United States.[1–18] Nearly 90% of 703 applicants for life insurance had

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From the Department of Pathology, Truman Medical Center (GS), and the Office for Health Services & Public Health Outcomes Research, Department of Biomedical and Health Informatics (AJB), University of Missouri-Kansas City School of Medicine, Kansas City, MO; and Heritage Laboratories International Inc., Olathe, KS (GS).

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Corresponding author: Gurmukh Singh, MD, PhD, MBA, Georgia Regents University, 1120 15th St., Augusta, GA 30912 (E-mail: gurmukhsinghmdphd@yahoo.com).

serum 25-hydroxyvitamin D concentration below 30 ng/mL.[18] The vast majority of these individuals were outwardly healthy and represented the "normal" US adult population. Most of an individual's vitamin D requirement may be met through synthesis of vitamin D from 7-dehydrocholesterol in the skin through exposure to sunlight, yet most people have serum concentration of 25-hydroxyvitamin D in the subnormal range, probably because of inadequate sun exposure, and require treatment with supplemental vitamin D.[17]

Vitamin D deficiency is strongly linked to rickets in children and osteomalacia in adults.[19–21] Other disorders associated with vitamin D deficiency include an increase in all-cause mortality, risk of falls, fractures, muscle weakness, pain and arthritis in the elderly, psoriasis, infections, poor oral health, cardiovascular disease, diabetes, multiple sclerosis, and cancers.[22–55] The findings regarding nonskeletal issues are based mostly on observational studies, and the validity of observational studies has been questioned because of a lack of confirmation by randomized controlled trials.[56,57]

There is universal consensus about the role of vitamin D in preventing rickets and osteomalacia, and vitamin D intake of 800 IU/day may be sufficient to protect bone health in healthy subjects. In a meta-analysis of 40 studies, Bolland et al[58] concluded that vitamin D and calcium administration reduced the incidence of hip fractures among institutionalized individuals but did not find any other beneficial effect from vitamin D supplementation. However, the average and median doses analyzed in the studies were 1060 and 800 IU/day, respectively, and serum concentrations of 25-hydroxyvitamin D of 20 ng/mL were considered sufficient. Only one of the 40 trials used a dose of >2000 IU/day. It could be argued that the subjects were deficient in vitamin D and received inadequate supplementation. Proponents of nonbone benefits of vitamin D supplementation recommend much higher doses; for example, Garland et al[4] stated that a serum concentration of 25-hydroxyvitamin D of 60 to 80 ng/mL may be needed to reduce cancer risk. Similarly, Ginde et al[59] reported protective effect of vitamin D from upper respiratory infections at 25-hydroxyvitamin D serum concentrations of >30 ng/mL.

The recommended daily allowance (RDA) for vitamin D was revised from 400 IU/day to 600 to 800 IU/day. Given the high prevalence of vitamin D deficiency, however, it is likely that the revised recommendation is insufficient for the general population, let alone patients.[5,18,32,60–68] Vitamin D need among healthy people for bone health is likely to be different from that of the population seeking health care, particularly if the role of vitamin D in nonskeletal health is accepted.[5,64–68]

Given the level of uncertainty about the recommended dose of vitamin D, we examined the responses of patients to vitamin D replacement under the usual circumstances of health care and analyzed factors affecting the response to treatment using changes in serum concentrations of 25-hydroxyvitamin D as the indicator of response. In 3885 pairs of observations, 25-hydroxyvitamin D concentrations before and after treatment and the average daily dose of vitamin D administered were analyzed. We analyzed averages, medians, and multiple linear regressions to ascertain statistically significant factors affecting the response to treatment. We arrived at a robust predictive equation for estimating the daily dose of vitamin D needed to effect a given change in serum concentrations of 25-hydroxyvitamin D.

Methods

This study was undertaken at a 2-campus, medical school–affiliated hospital (University of Missouri–Kansas City School of Medicine) with 592 beds (300 acute care beds). The main campus is a level 1 trauma center in the inner city. The second campus provides mainly family medicine and long-term care (nursing home) in a suburban setting. The hospitals serve as the safety net hospitals for Kansas City and Jackson County, Missouri, and the majority of the patients are uninsured. The average age of the patients is about 56 years, and 943 female and 384 male patients were analyzed for the study. The average body mass index (BMI) was 31.5 kg/m^2. Common diagnoses among ambulatory patients included overweight/obesity, hypertension, diabetes mellitus, hyperlipidemia/dyslipidemia, chronic obstructive airway disease, gastroesophageal reflux disease, chronic renal disease, hypothyroidism, and substance abuse. Almost all patients had multiple diagnoses. Nursing home patients had multiple chronic diseases including multiple sclerosis; stroke; overweight/obesity; diabetes mellitus; hypothyroidism; chronic obstructive pulmonary disease; dementia; psychiatric disorders; debilitating

cardiovascular, renal, and hepatic insufficiency; and urinary and fecal incontinence interspersed with infections such as *Clostridium difficile*, urinary infection, and pneumonia.

Assays for 25-hydroxyvitamin D were done in a Clinical Laboratory Improvement Amendments–certified laboratory using and Advia Centaur XP analyzer from Siemens. The immunoassay measures both cholecalciferol (D3) and ergocalciferol (D2), and the sum of results of the 2 were reported. We understand that different methods generate different results and the methods have not been harmonized; however, the same method was used for the assays and we examined change in serum concentrations in response to treatment. We examined the test volume for serum 25-hydroxyvitamin D concentrations in 2007 to 2012 and determined the mean serum 25-hydroxyvitamin D concentration in each year and the distribution of 25-hydroxyvitamin D concentration of <30, <20, <12, and >150 ng/mL (1.0 ng/mL = 2.496 mmol/L). We examined the medical records of 2485 patients who had serum 25-hydroxyvitamin D concentrations recorded between June 20 and August 31, 2012, for details of serum 25-hydroxyvitamin D concentrations and doses of vitamin D administered, and we calculated the average daily dose between 2 measurements of 25-hydroxyvitamin D during the entire duration of the patients' contact with Truman Medical Centers. We recorded the patients' age, sex, BMI, serum creatinine and serum albumin concentrations, and nursing home residence versus ambulatory care status. The data were analyzed to determine the average and median doses of vitamin D per day that resulted in (1) a decrease in serum 25-hydroxyvitamin D or no change, (2) any increase in serum 25-hydroxyvitamin D concentration, or (3) an increase in serum 25-hydroxyvitamin D concentration of ≥10 ng/mL.

To understand the relationship between age, sex, nursing home residence, serum albumin concentration, BMI, creatinine, and starting serum concentration of 25-hydroxyvitamin D when predicting change in serum 25-hydroxyvitamin D concentration and the concentration after treatment (end), multiple linear regression analyses were performed. The regression analyses included all 3885 encounters with complete data. When variables in the whole model were not statistically significant, they were removed using a stepwise procedure until we arrived at reduced models that included only statistically significant ($\alpha = 0.05$) predictors. Some patients had multiple episodes of treatment and were represented twice or more; therefore we also analyzed the data by removing multiple readings from the same patient and keeping only the data from the last episode of treatment.

The patients were sorted into 3 racial groups: white, black, and other. The mean serum concentrations of 25-hydroxyvitamin D at the start of each episode of treatment were calculated for the 3 groups. The doses administered that resulted in (1) no change or decrease in serum concentrations of 25-hydroxyvitamin D, (2) any increase, and (3) an increase of ≥10 ng/mL were determined. The results were examined for clinically meaningful difference among the races.

The institutional review board of the University of Missouri–Kansas City and the Privacy Board of Truman Medical Centers approved the study. The institutional review board waived the requirement for consent from subjects.

Results

The testing volume for 25-hydroxyvitamin D increased from <300 to >12,000/year in 2007 to 2012, without meaningful change in the average serum 25- hydroxyvitamin D concentrations (Figure 1 and Table 1). The proportions of patients in each of the subgroups with serum 25-hydroxyvitamin D concentrations of <30, <20, <12, and >150 ng/mL were not different to any clinically meaningful extent, although there was a statistically significant ($P < .05$) decline in mean serum 25-hydroxyvitamin D concentrations and an increase in the proportion of patients with serum 25-hydroxyvitamin D concentrations of <12, <20, and <30 ng/mL.

Of the 2485 patients reviewed, 1327 (943 women, 384 men) had at least 2 serum 25-hydroxyvitamin D concentrations with documentation of treatment after the first test. We excluded 1158 patients (46.6%) from further analysis because they either had only one determination of serum concentration of 25-hydroxyvitamin D or had multiple concentrations documented but there was no evidence of a prescription for replacement vitamin D or there was documentation of a lack of compliance with treatment. A valid episode of treatment required 2 serum 25-hydroxyvitamin D

Figure 1. Annual volume of 25-hydroxyvitamin D testing and mean serum concentrations of 25-hydroxyvitamin D in each year. The year-to-year changes in the mean concentrations (inset) of 25-hydroxyvitamin D are statistically significantly different ($P < .05$). The testing volume increased from <300 to >12,000 per year without any improvement in the outcome of average serum concentrations of 25-hydroxyvitamin D, despite the providers' prescription being in keeping with recommended doses of vitamin D, suggesting that the recommended doses were inadequate.

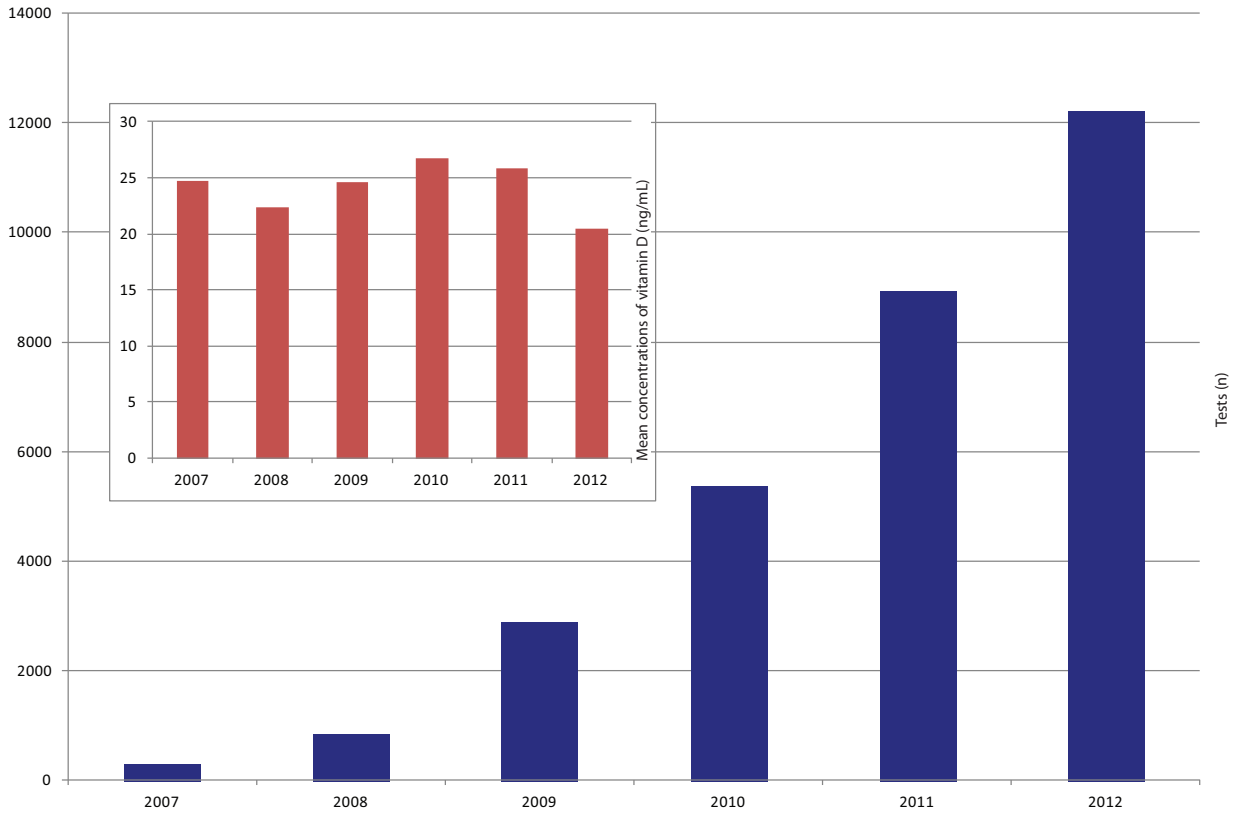


Table 1. Number of Tests for Serum 25-Hydroxyvitamin D and Serum Concentrations of 25-Hydroxyvitamin D

	Serum 25-Hydroxyvitamin D Concentration (ng/mL)				
Year	<12	<20	<30	>150	Total Tests (n)
2007	17.24	48.62	71.38	0.34	290
2008	21.04	47.4	75.77	0	846
2009	16.65	39.01	69.19	0	2,889
2010	15.53	35.55	63.27	0.04	5,358
2011	16.81	38.15	65.14	0.02	8,910
2012	33.11	60.83	82.22	0.07	12,194

Data are percentages unless otherwise indicated. The number of serum 25-hydroxyvitamin D tests done increased from 290 in 2007 to 12194 in 2012. The percentage of patients with serum concentrations of 25-hydroxyvitamin D <12, 20, 30 or >150 ng/mL did not change appreciably. If anything the serum25-hydroxyvitamin D concentrations decreased during the period of observation, again attesting that patients were undertreated.

concentrations with documentation of treatment between the 2 measurements. From the prescribed dose and the interval between 2 laboratory measurements of serum 25-hydroxyvitamin D, the average daily dose of vitamin D was calculated.

There were 3885 episodes of 2 vitamin D measurements with documented treatment between the 2 readings. There were an average of 2 valid episodes for each ambulatory patient and 8 for nursing home patients. Among 1552 episodes, vitamin D treatment was associated with a decrease in serum 25-hydroxyvitamin D concentration or no change. The average and median daily doses of vitamin D in this group were 1907 and 1000 IU/day, respectively. In 2333 episodes of treatments there was an increase (any increase) in serum 25-hydroxyvitamin D concentrations, and the average and median doses of vitamin D were 4707 and 4000 IU/day, respectively. An increase of ≥10 ng/mL was seen in

Table 2. Average (Median) Daily Doses of Vitamin D (IU/day) and Changes in Serum 25-Hydroxyvitamin D Concentrations after Treatment

	Average Dose ± Standard Deviation (Median)		
Population	Decrease or No Increase	Any Increase	Increase ≥10 ng/mL
All	1907 ± 1771 (1000)	4707 ± 3856 (4000)	5682 ± 4323 (4800)
Ambulatory	2154 ± 1716 (2000)	4229 ± 3637 (3976)	5092 ± 4092 (4000)
Nursing home	1427 ± 1709 (800)	6103 ± 4131 (5448)	7574 ± 4505 (6597)

An average daily dose of about 2000 IU/day did not register a positive change in serum concentrations of 25-hydroxyvitamin D. Doses of about 4000 to 7000 IU/day were needed for meaningful increases in serum concentrations of 25-hydroxyvitamin D. The observed doses that resulted in positive changes in serum concentrations of 25-hydroxyvitamin D are far greater than the doses recommended by national agencies.

1236 observations; average and median daily doses of vitamin D were 5682 and 4800 IU/day, respectively. The corresponding values for ambulatory and nursing home patients are given in Table 2.

In 68.5% episodes the serum concentration of 25-hydroxyvitamin D was <30 ng/mL before treatment. This included patients who were treated, and some had multiple cycles of treatment. After treatment, the proportion of patients with a serum 25-hydroxyvitamin D concentration <30 ng/mL was 55.3%, a drop of only 13.2 percentage points. On average, there was an increase of only 5.3 ng/mL in concentrations of serum 25-hydroxyvitamin D after treatment. The responses of the various subgroups of patients to the average daily doses are given in Table 3.

Predicting Change in Serum Concentrations of 25-Hydroxyvitamin D from Before to After Treatment

A multiple linear regression analysis was performed to identify the best model for predicting the change from baseline to post-treatment serum concentrations of 25-hydroxyvitamin D in the 3885 valid encounters. Table 4 displays regression coefficients for the full model and reduced model, which includes only statistically significant ($P < .05$) predictors of change. The full model ($R^2 = 0.424$; $P < .001$) and reduced model ($R^2 = 0.423$) explained about 42% of the variability in change in serum 25-hydroxyvitamin D concentrations. The equation for predicting change in serum 25-hydroxyvitamin D concentrations (derived from the reduced model) is:

$$\begin{aligned}\text{Change} = {} & 0.07(\text{Age}) - 0.20(\text{BMI}) \\ & + 0.002(\text{Dose [IU/day]}) \\ & + 1.74(\text{serum albumin [g/dL]}) \\ & - 0.62(\text{starting 25-hydroxyvitamin D serum concentration}) + 8.52\end{aligned}$$

The dose required for a given desired change in serum 25-hydroxyvitamin D concentration is:

Table 3. Average Responses of Various Subsets of Patients to Average Daily Doses of Vitamin D Treatment

				Average Concentration (ng/mL)		Concentration <30 ng/mL (%)	
Population	Patients (n)	Observations (n)	Average Dose (IU/day)	Before Treatment	After Treatment	Before Treatment	After Treatment
Total	1327	3885	3588	25.2	30.5	68.5	55.3
Ambulatory	1183	2763	3460	22.4	29.1	75.7	61.1
Women	839	1947	3494	22.5	29.1	76	62.0
Men	344	816	3375	22.4	29.2	74.9	59.1
Nursing Home	144	1122	3907	32.2	34.1	47.1	41.0
Women	104	820	2902	32	33.9	48.8	42.4
Men	40	302	3918	32.5	34.4	42.7	37.1

The average increase in serum concentrations of 25-hydroxyvitamin D, with an average dose of 3588 IU/day, for the whole population (total observations = 3885) was 5.3 ng/mL.

Table 4. Regression Coefficients Predicting Change in Serum 25-Hydroxyvitamin D Concentration: Full and Reduced Models for All Patients and All 3885 Observations

			95% Confidence Interval	
	B	*P* Value	Lower	Upper
Full model				
Age	0.092	<.001*	0.05	0.13
Sex	0.647	.269	−0.50	1.8
BMI	−0.200	<.001*	−0.26	−0.14
Nursing Home	1.390	.057	−0.04	2.82
Albumin	1.457	.013*	0.28	2.44
Creatinine	−0.462	.209	−1.18	0.26
Dose of vitamin D	0.002	<.001*	0.002	0.002
Starting vitamin D	−0.615	<.001*	−0.65	−0.58
Constant	7.838	.008*	2.02	13.66
Reduced model				
Age	0.074	<.001*	0.04	0.11
BMI	−0.202	<.001*	−0.26	−0.14
Albumin	1.739	.001*	0.73	2.75
Dose of vitamin D	0.002	<.001*	0.002	0.002
Starting vitamin D	−0.622	<.001*	−0.66	−0.59
Constant	8.521	.003*	2.86	14.18

*Statistically significant ($P < .05$).
BMI, body mass index.

([8.52 – Desired change in serum 25-hydroxyvitamin D concentration] + [0.07 × Age] – [0.20 × BMI] + [1.74 × serum albumin {g/dL}] – [0.62 × Starting serum 25-hydroxyvitamin D concentration]/−0.002).

For each additional IU of vitamin D administered we anticipate a 0.002-ng/mL increase in serum 25-hydroxyvitamin D. For every additional 1.0 ng/mL of 25-hydroxyvitamin D before treatment, there will be a decrease of 0.62 ng/mL in the concentration after treatment. For every 1.0-unit increase in BMI there will be a reduction in 25-hydroxyvitamin D of 0.20 ng/mL. For every 1.0-g/dL increase in albumin we expect a 25-hydroxyvitamin D increase of 1.74 ng/mL. For every additional year of life (age) there is a 25-hydroxyvitamin D increase of 0.07 ng/mL, or, more correctly, the need for a replacement dose of vitamin D is lower with increasing serum albumin concentration and age. The same explanations apply to all of the regression analyses.

Predicting End (Post-treatment) Serum 25-Hydroxyvitamin D Concentration

A similar multiple linear regression analysis was performed to identify the best predictive model for serum 25-hydroxyvitamin D after treatment (end). Table 5 displays the regression coefficients for the full and reduced models. Both models explained about 24% of the variability in post-treatment serum 25-hydroxyvitamin D concentrations ($R^2 = 0.236$; $P < .001$). The equation for predicting serum 25-hydroxyvitamin D concentration after treatment is:

End serum 25-hydroxyvitamin D concentration = 0.07(Age) – 0.20(BMI) + 0.002(Dose) + 1.75(Serum albumin [g/dL]) + 0.38(Starting 25-hydroxyvitamin D concentration) + 8.48.

Nursing Home versus Ambulatory Patients

Bivariate comparisons were performed to determine whether the key factors used to predict serum 25-hydroxyvitamin D outcomes differed between nurs-

Table 5. Regression Coefficients Predicting End (after Treatment) Serum 25-Hydroxyvitamin D Concentration

			95% Confidence Interval	
	B	*P* Value	Lower	Upper
Full model				
Age	0.092	<.001*	0.05	0.13
Sex	0.616	.293	−0.53	1.77
BMI	−0.201	<.001*	−0.26	−0.14
Nursing home	1.349	.065	−0.08	2.78
Albumin	1.378	.012*	0.30	2.46
Creatinine	−0.467	.205	−1.19	0.26
Dose of vitamin D	0.002	<.001*	0.002	0.002
Starting vitamin D	0.384	<.001*	0.35	0.42
Constant	7.853	.008*	2.03	13.68
Reduced model				
Age	0.074	<.001*	0.04	0.11
BMI	−0.203	<.001*	−0.26	−0.15
Albumin	1.749	.001*	0.74	2.76
Dose of vitamin D	0.002	<.001*	0.002	0.002
Starting vitamin D	0.074	<.001*	0.04	0.11
Constant	−0.203	<.001*	−0.26	−0.15

Full and reduced models for all patients and all 3885 observations are included.
*Statistically significant ($P < .05$).
BMI, body mass index.

ing home and ambulatory patients. χ^2 test was used to compare the sexes. Independent sample *t* tests were used for the continuous variables. When the comparisons between ambulatory and nursing home patients failed to meet the assumption of equality of variances, a Mann-Whitney *U* test was used. Table 6 displays descriptive statistics and *P* values for these bivariate comparisons. For each variable there was a statistically significant difference between nursing home and ambulatory encounters ($P < .05$ for both). Therefore, we separated the nursing home and ambulatory encounters and performed regression analyses for each subgroup.

Nursing Home Patients

The regression coefficients for the full and reduced models for predictors of change in serum 25-hydroxyvitamin D concentrations were essentially identical and explained about 60% of the variability ($R^2 = 0.595$; $P < .001$). The equation for predicting change in serum 25-hydroxyvitamin D concentrations (derived from the reduced model) is:

Change in serum 25-hydroxyvitamin D concentration
= 0.002(Dose [IU/day]) – 0.23(BMI)
– 0.79(Starting 25-hydroxyvitamin D serum concentration) + 28.01

We performed a multiple linear regression analysis for predicting the end concentration of serum 25-hydroxyvitamin D among the 1122 nursing home encounters. Coefficients for the full and reduced models for predictors of the end serum 25-hydroxyvitamin D concentration were virtually identical and explained about 16% of the variability ($R^2 = 0.160$; $P < .001$).

End serum concentration of 25-hydroxyvitamin D
= 0.002(Dose [IU/day]) – 0.23(BMI)
+ 0.21(Starting 25-hydroxyvitamin D serum concentration) + 28.28

Ambulatory Patients

A multiple linear regression analysis was performed to predict the change from baseline to post-treatment serum concentrations of 25-hydroxyvitamin D among the 2763 ambulatory encounters. The regression coefficients for the full model and the reduced model, which includes only statistically significant predictors of change in serum 25-hydroxyvitamin D concentration, were again nearly identical and explained about 36% of the variability ($R^2 = 0.364$; $P < .001$). The equation for predicting change in serum 25-hydroxyvitamin D concentration is:

Table 6. Bivariate Comparisons of Nursing Home and Ambulatory Patient Encounters

	Ambulatory		Nursing Home		
	No.	Mean (SD)	No.	Mean (SD)	*P* Value
Age*	2763	56.0 (12.8)	1122	73.1 (14.1)	<.001†
BMI	2763	33.4 (8.9)	1122	30.4 (9.1)	<.001†
Vitamin D concentration					
Start*	2763	22.4 (15.1)	1122	32.2 (13.8)	<.001†
End*	2763	29.1 (19.8)	1122	34.1 (13.8)	<.001†
Change	2763	6.7 (21.5)	1122	1.9 (19.8)	<.001†
Dose*	2763	3458.2 (3228.7)	1122	3906.6 (3997.8)	.018†
Creatinine*	2754	1.17 (0.77)	1122	1.00 (0.62)	<.001†
Albumin*	2735	3.8 (0.5)	1118	3.3 (0.5)	<.001†
Sex‡					
Female		1947 (70.5)		820 (73.1)	.113
Male		813 (29.5)		302 (26.9)	

*Statistically significant ($P < .05$).
†Comparisons fail to meet the assumption of equal variances.
‡Data for Sex are n (%).
BMI, body mass index; SD, standard deviation.

Change in serum 25-hydroxyvitamin D concentration = 0.003(Dose [IU/day]) – 0.21(BMI) – 0.59(Starting 25-hydroxyvitamin D serum concentration) + 1.87(Albumin [g/dL]) + 0.12(Age [years]) + 4.22

The coefficient for the dose of vitamin D is 0.003 for ambulatory patients compared with 0.002 for nursing home patients. This is in keeping with the higher doses needed for nursing home patients.

The regression coefficients for the full and reduced models of ambulatory patients were essentially similar and explained about 25% of the variability in end serum 25-hydroxyvitamin D concentration ($R^2 = 0.247$; $P < .001$).

End serum 25-hydroxyvitamin D concentration = 0.003(Dose [IU/day]) – 0.21(BMI) + 0.41(Starting 25-hydroxyvitamin D serum concentration) + 1.87(Albumin [g/dL]) + 0.12(Age [years]) + 4.22

When multiple observations of a given patient were removed from regression analyses and only the last observation in the set was kept, the results for ambulatory patients were not meaningfully different from those presented above. For nursing home patients the small number of observations did not allow for meaningful analysis.

The comparative findings among the 3 racial groups are presented in Table 7. The average doses resulting in (1) no increase or decease in serum concentrations of 25-hydroxyvitamin D, (2) any increase, and (3) increase of ≥10 ng/mL were not different among the 3 races to any clinically meaningful extent. The baseline serum concentrations of 25-hydroxyvitamin D before each episode of treatment also were not meaningfully different among the 3 groups.

Unstructured observations included the following:

1. The recommended dose of 800 IU/day for nursing home residents and ambulatory patients is generally inadequate for maintaining normal serum concentrations of 25-hydroxyvitamin D. An example of such an observation in a nursing home patient is shown in Figure 2.
2. Acute illnesses tend to deplete serum 25-hydroxyvitamin D concentrations, and despite documented deficiency of serum 25-hydroxyvitamin D and hypocalcaemia, acutely ill patients often did not receive supplemental vitamin D.
3. Increase in weight tended to reduce serum concentrations of 25-hydroxyvitamin D; the reverse was also true.

Discussion

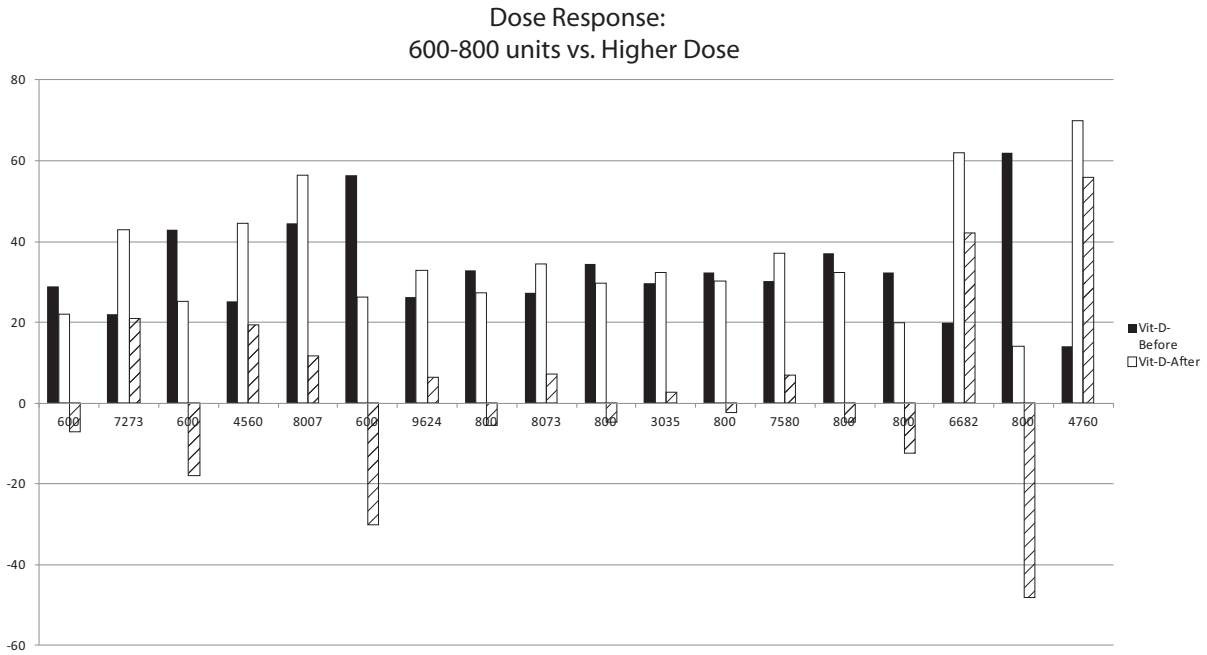
There is controversy about the "normal, healthy" or required serum concentrations of 25-hydroxyvitamin D. Values >30 to 32 ng/mL are considered to be normal or adequate. 25-Hydroxyvitamin D serum concentrations of 20 to 30 ng/mL are con-

Table 7. Comparison of Starting Serum Levels of 25-Hydroxyvitamin D and Average Doses Resulting in Decrease or No Increase, Any Increase, or Increase of ≥10 ng/mL between Races

	White	Black	Other
Patients (n)	710	521	96
Episodes (n)	2227	1385	273
Results of average dose (mean ± SD)			
Decrease or no change	1995 ± 1830	1774 ± 1689	1868 ± 1646
Any increase	4827 ± 3865	4540 ± 3781	4554 ± 4107
Increase of ≥10 ng/mL	5760 ± 4362	5539 ± 4216	5744 ± 4536
25-hydroxyvitamin D serum concentration (ng/mL) at start of treatment episode	25.5 ± 15.0	25.3 ± 15.9	23.0 ± 14.8

The differences between the races do not seem to be clinically meaningful.
SD, standard deviation.

Figure 2. Dose response in a patient. The graph displays the starting concentration (black), end concentration (white), and change (diagonal lines) in 25-hydroxyvitamin D concentration in one patient given the recommended doses of 600 to 800 IU/day interspersed with treatment with higher doses. Doses administered are given below each episode of treatment. In this purposely selected nursing home patient, each episode of treatment with the Geriatric Society–recommend dose resulted in decline in serum 25-hydroxyvitamin D concentration, and each episode of treatment with a higher dose increased the serum concentration of 25-hydroxyvitamin D, suggesting that the Geriatric Society–recommended dose was inadequate. The patient was admitted to the nursing home at the age of 47 with a 10-year history of multiple sclerosis and had paraplegia, urinary retention with repeated infections, fecal incontinence, pressure ulcers, gastroesophageal reflux, type 2 diabetes mellitus, body mass index of 29.8 kg/m^2, rheumatoid arthritis, lactose intolerance, hypertension, hyperlipidemia, history of vitamin B12 and folate deficiency, depression, degenerative joint disease, and dysphagia with risk of aspiration. She made multiple attempts to live at home but was readmitted and developed heart failure and experienced episodes of renal and respiratory failure often associated with sepsis. She died at the age of 54 due to progressive heart failure.



sidered to be low, concentrations of 12 to 20 ng/mL are considered to be insufficient, and values <12 ng/mL represent a deficiency.[1–17] The US population of apparently healthy people has a much higher prevalence of low, insufficient, or deficient concentrations than expected, considering that usually normal laboratory values are defined as the central 95% of the observations in a "healthy" population; however, this concept does not always apply.[18,69,70] The underexposure to sun among the US population may be akin to the universal hookworm infestation in poor, rural parts of the world. Just as using the central 95% of hemoglobin concentrations in the hookworm-infested population would be inappropriate, it may be inappropriate to use the prevalent serum concentrations of 25-hydroxyvitamin D in the United States to define normal or reference concentrations. Another analogy is the reference concentrations of cholesterol: the "normal" values are based on desired values rather than the central 95% of the values in the United States. Similarly, just because the average BMI of the subjects in our study was 31 kg/m^2 does not warrant using a BMI of 31 kg/m^2 as "normal."

The prevalence of low serum concentrations of 25-hydroxyvitamin D has been documented in the general population through different sampling methods. An analysis of 703 applicants for life insurance revealed high prevalence of low serum concentrations of 25-hydroxyvitamin D. These samples were collected in August and were drawn from all over the United States. Serum concentrations of 25-hydroxyvitamin D are generally higher in summer; however, in this sample of apparently healthy

individuals nearly 90% had serum concentrations of 25-hydroxyvitamin D <30 ng/mL.[18] Analyzing data from the National Health and Nutrition Examination Survey, Ginde et al[59] reported increasing incidence of low serum concentrations of 25-hydroxyvitamin D and noted that 83% of the subjects had serum concentrations <30 ng/mL.

The widespread presence of low serum concentrations of 25-hydroxyvitamin D is the usual reason for testing patients at the Truman Medical Center. Determination of serum concentrations of 25-hydroxyvitamin D is done as part of adult health maintenance. The testing frequency among nursing home patients is driven by the recommendations of the American Geriatrics Society. It should be added that the American Geriatrics Society recommendations issued in 2013 discuss strategies to achieve total vitamin D input of 4000 IU/day to reduce the risk for falls or fall-related injuries among nursing home patients.[71]

The likely causes of widespread deficiency are reduced exposure to sunlight because of decreased outdoor work and activity, increased attention to the role of sun exposure as a contributor to skin cancers and increased use of sunscreens, widespread overweight/obesity, and perhaps a reduction in the consumption of milk.[72–78] Overweight/obesity reduces serum concentrations of 25-hydroxyvitamin D through dilution of this fat-soluble vitamin in the adipose tissue; as presented here, overweight/obese individuals require higher replacement doses of vitamin D.[76–78]

The need for higher doses of vitamin D in nursing home patients is probably due to a lack of exposure to sun, since increased age was not a negative factor in the response to vitamin D treatment.[78]

Using change as the dependent variable has been faulted by experts in statistical analysis.[79] However, the results of regression analyses were not meaningfully different when using change and post-treatment serum concentrations of 25-hydroxyvitamin D as the dependent variables. The only difference was in the direction of the effect of baseline 25-hydroxyvitamin D concentration, which was a negative predictor of change and a positive predictor of post-treatment 25-hydroxyvitamin D concentrations, and this is in keeping with mathematical principles.

As expected, the dose of vitamin D is the most dominant factor in determining the change in serum 25-hydroxyvitamin D concentrations when examining averages and regression analyses. If we were to ignore other factors, the regression equation suggests that a dose of 5000 IU/day would be needed to effect a 10-ng/mL increase in 25-hydroxyvitamin D serum concentration. The figure of 5000 IU/day was calculated from the regression analysis revealing that each IU of vitamin D results in a 0.002-ng/mL increase in 25-hydroxyvitamin D serum concentration ([10/0.002] = 5000). This finding is remarkably similar to the conclusion from looking at averages, which yielded a value of 5682 IU/day for an increase of ≥10 ng/mL. This finding is also in keeping with the recommendations of the Endocrine Society.[3] Two excerpts from the recommendations of the society are given below. The first quotation deals with general subjects.

"We suggest that all adults who are vitamin D deficient be treated with 50,000 IU of vitamin D2 or vitamin D3 once a week for 8 weeks or its equivalent of 6000 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 1500 to 2000 IU/d."[3]

The Endocrine Society recommendation relevant to the nursing home patients reads: "In obese patients, patients with malabsorption syndromes, and patients on medications affecting vitamin D metabolism, we suggest a higher dose (two to three times higher; at least 6000 to 10,000 IU/d) of vitamin D to treat vitamin D deficiency to maintain a 25(OH)D level above 30 ng/mL, followed by maintenance therapy of 3000 to 6000 IU/d."[3]

One item missing from our analysis is the duration of treatment. This could not be included because of the wide variation in the intervals between laboratory determinations of vitamin D. However, a common interval was about 3 months. Hence, we recommend that patients with serum 25-hydroxyvitamin D concentrations <30 ng/mL be treated with 5000 IU/day for 3 to 6 months followed by retesting; those needing maintenance therapy should be prescribed 2000 to 4000 IU/day, depending on other clinical factors. A more personalized dose for the desired change may be estimated from the predictive equations for nursing home and ambulatory patients.

The low concentrations and increased need for vitamin D are probably due in part to the high prevalence of overweight/obesity.[74–76] One of our unstructured observations was that gain in weight

tended to reduce 25-hydroxyvitamin D serum concentrations and weight loss improved the response to vitamin D. In the regression analyses, BMI was a significant negative predictor of the change in serum 25-hydroxyvitamin D concentrations and the concentration after treatment. This finding may be explained by the dilution of 25-hydroxyvitamin D in body fat, since vitamin D is fat soluble.[76,77]

The finding that patients with low serum albumin concentrations required higher doses of replacement vitamin D probably reflects multiple issues. Low serum concentrations of albumin and 25-hydroxyvitamin D are both markers of poor nutrition. Low serum albumin concentrations may also indicate hepatocellular dysfunction and the inability of the liver to convert vitamin D into 25-hydroxyvitamin D. Albumin is also a carrier protein for 25-hydroxyvitamin D, and low serum concentrations of albumin may result in low serum concentrations of 25-hydroxyvitamin D because of a deficiency of a carrier protein in a manner similar to the low serum concentrations of 25-hydroxyvitamin D caused by lower levels of a specific vitamin D binding protein among blacks in America.[80,81]

The RDA for vitamin D was revised from 400 to 800 IU/day for most adults.[12,17,31] A similar dose has been found to be sufficient to prevent fractures.[82,83] The American Geriatrics Society recommended a vitamin D dose of 800 IU/day (and calcium) for nursing home patients; however, our observations showed this to be inadequate for maintaining serum concentrations of 25-hydroxyvitamin D let alone correcting low concentrations; thus repeated treatments with high doses are necessary, as illustrated in Figure 2. As mentioned earlier, since the beginning of this study, the American Geriatrics Society has revised the recommendation to increase the intake to 4000 IU/day.[71] It may be better to provide a constant dose of 2000 to 4000 IU/day, after correcting the deficiency with a higher dose of 5000 IU/day, and monitor the serum concentrations of 25-hydroxyvitamin D once or twice a year, rather than the current practice of testing every 3 months.[22,54,62] The predictive equations offered in this article may facilitate a more personalized treatment. While high doses given at less frequent intervals may be adequate to rectify deficiency and maintain normal concentrations, regular dosing may be better for compliance and is a more physiological approach.[83,84]

The lack of response to generally recommended supplementation might be due to poor compliance. We recognize the issue of nonadherence to treatment as having the potential for making the response to treatment seem like an inadequate response. We scrutinized the medical records for any documentation of nonadherence to treatment, with the understanding that medical records are often incomplete. However, about 47% of the patients were excluded in part because of documentation of noncompliance. When patients were prescribed higher doses, their serum concentrations of 25-hydroxyvitamin D did increase, and we have no reason to believe that prescribing higher doses would improve compliance. Please note that compliance was not an issue in the nursing home; however, the data from nursing home patients indicated the need for even higher doses than those required by ambulatory patients.[78] In nursing home patients, among whom the administration of medication is better controlled, the same observation held true: generally recommended doses of vitamin D were inadequate for maintaining normal concentrations or correcting states of deficiency. It is noteworthy that the average increase in serum concentrations of 25-hydroxyvitamin D were only 1.9 ng/mL for each episode of treatment among nursing home patients, as shown in Table 3. This outcome was the direct result of complying with the American Geriatrics Society recommendations of prescribing 600 to 800 IU of vitamin D plus calcium. This treatment often resulted in a decrease in serum concentrations of 25-hydroxyvitamin D and the prescription of higher doses in response to the change. Such cycles of recommended and high doses were repeated often, as illustrated in Figure 2.

The regression analyses suggest that the significant predictors of change in serum 25-hydroxyvitamin D concentrations differ between nursing home and ambulatory patients; therefore, we believe it is prudent to use different treatment regimens for the 2 populations. We suggest that the predictive equations presented here provide a useful guide for estimating the effective doses of vitamin D for each population.

Our unstructured observation that acute illnesses tend to deplete vitamin D and result in lower serum concentrations of 25-hydroxyvitamin D in affected patients is supported by more systematic studies of the subject, as reported by Jeng et al.[85] Other studies reported adequate response to treat-

ment with Institute of Medicine–recommended doses of about 800 IU/day; however, the subjects in these studies were generally healthy individuals. For example, studies by Gallagher et al[82] and Bischoff-Ferrari et al[86] reported adequate response to supplementation with 800 IU/day in preventing fractures. However, the study populations consisted of "165 healthy postmenopausal white women," not patients with multiple diagnoses that were the subjects in this study.[82]

It has been recognized that blacks have lower serum concentrations of 25-hydroxyvitamin D. A putative explanation for this is the lower levels of vitamin D binding protein in blacks compared with whites.[78] Another likely explanation is the reduced effectiveness of sunlight because of skin pigmentation. We did not observe clinically meaningful differences in 25-hydroxyvitamin D serum concentrations at the start of treatment among the 3 races. The pretreatment concentrations reported here represent the serum concentrations of 25-hydroxyvitamin D before an episode of treatment, keeping in mind that many patients received vitamin D before that. The average doses of vitamin D resulting in (1) decrease or no increase in serum concentrations of 25-hydroxyvitamin D, (2) any increase in serum concentrations, and (3) an increase of ≥10 ng/mL were also not meaningfully different among the 3 racial groups (Table 7).

This retrospective, observational study has a number of limitations, as is generally the case with such studies. The method for measuring serum 25-hydroxyvitamin D changed over the 6-year period, and values generated by different methods often are not comparable. However, the change in methods is not likely to have affected the change in concentrations at the beginning and end of treatment, which was usually about 3 months. Adherence to the medication regimen was often less than optimal among the ambulatory patients; however, higher doses did result in a greater increase in serum concentrations of 25-hydroxyvitamin D and, as noted above, we excluded noncompliant patients from the study. The results from the nursing home population, where compliance is nearly guaranteed, did not differ markedly from those of the ambulatory population. This observation supports the notion that noncompliance probably does not explain the poor response to treatment and that the small increase in serum 25-hydroxyvitamin D concentrations after treatment is due to prescribing inadequate amounts of vitamin D.

One more drawback of the study is the lack of a uniform duration of treatment. There was considerable variability in the duration of treatment, and often high doses were given, usually to nursing home patients, followed by a gap in treatment before the next serum 25-hydroxyvitamin D concentration measurement. Three months was the usual interval between laboratory tests, especially for nursing home patients.

An additional weakness is related to the predictive equations; some patients are represented multiple times and others are represented only once. Nevertheless, this is not an issue because analysis of the data using only one observation per patient gave results similar to the whole data set for ambulatory patients. However, this modification to the analysis reduced the number of observations in nursing home patients so much that the results were not meaningful.

The observational, retrospective nature of the study is also its strength; an unselected population receiving routine care was analyzed. The many inclusion and exclusion criteria in randomized trials are not applicable in the circumstances of usual health care delivery. The controversy about the dose of vitamin D needed for bone health in "healthy" people may not be applicable here because of multiple illnesses in the population examined. We submit that it is inappropriate to use the RDA of vitamin D intended to maintain the bone health of "healthy" people for the population seeking health care, and that predictive equations presented here, based on empirical data, provide a useful guide for personalized treatment.

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