Treatment of Vitamin D Deficiency in Predominantly Hispanic and Black Adolescents: A Randomized Clinical Trial

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Objectives To compare 3 different treatment regimens for vitamin D deficiency in minority adolescents and to explore factors that impact treatment efficacy.

Study design We conducted an 8-week, prospective, open-label, randomized clinical trial in an urban, academic, children's hospital. A total of 183 vitamin D-deficient adolescents, mean 25-hydroxyvitamin D or 25(OH)D 13.7 ± 3.9 ng/mL; mean age 16.6 ± 2.2 years, were randomized into 3 vitamin D3 (cholecalciferol) treatment arms: 50 000 IU/wk; 5000 IU/d; and 1000 IU/d. Serum 25(OH)D and vitamin D binding protein (VDBP) levels were measured pre-and posttreatment; 122 (67%) participants completed posttreatment measures. Complete-case and multiple-imputation, intention-to-treat analyses were performed.

Results Mean change in 25(OH)D level posttreatment was significantly different among the 3 arms, 24.9 ± 15.1 vs 21.0 ± 15.2 vs 6.2 ± 6.5 ng/mL, for 50 000 IU, 5000 IU, and 1000 IU doses, respectively, $P < .001$. Both high-dose treatments were effective in increasing the 25(OH)D level out of deficiency range ($\geq$20 ng/mL) in more than 80% of participants, and 60% remained deficient after low-dose treatment. Only 72%, 56%, and 2% achieved vitamin D sufficiency (>30 ng/mL) with 50 000 IU, 5000 IU, and 1000 IU doses, respectively, $P < .001$. Obese participants had substantially less mean change in 25(OH)D level after treatment than normal-weight participants, 13.7 ± 10.7 vs 21.9 ± 16.9 ng/mL, $P < .001$. Mean baseline VDBP level was almost twice as high in Hispanic compared with black participants ($P < .001$) and did not alter treatment response or change with treatment.

Conclusions Adult-sized adolescents require 8 weeks of high-dose cholecalciferol, at least 5000 IU/d, to correct deficiency. Obese adolescents have poorer response to treatment and may need higher doses than nonobese youth. Hispanic and black adolescents have different VDBP levels but similar treatment responses. *(J Pediatr 2016;170:266-72).*

Trial registration ClinicalTrials.gov: NCT01784029.

V itamin D has multiple skeletal and extra-skeletal effects.[1,2] Adolescence is a critical time for bone mass accrual, and low vitamin D levels are associated with low bone density and stress fractures in this age group.[3,4] Studies of US adolescents indicate that low vitamin D levels are associated with hypertension, hyperglycemia, and metabolic syndrome,[5-7] and some studies have shown improvement in hypertension and insulin resistance with vitamin D repletion.[8-10] In addition, studies of both clinical and national samples of US adolescents find that vitamin D deficiency is rising in prevalence, particularly among obese and darker-skinned youth.[11-14] Evidence informing guidelines for treatment of vitamin D deficiency in the adolescent age group is lacking; most treatment studies were conducted on infants and toddlers or adults.[15-17]

Serum 25-hydroxyvitamin D or 25(OH)D level is the best indicator of total body vitamin D status.[17] Commonly accepted definitions of vitamin D deficiency: 25(OH)D <20 ng/mL; insufficiency: 25(OH)D 20-30 ng/mL; and sufficiency: 25(OH)D >30 ng/mL are determined by outcomes related to bone metabolism, but higher levels may be needed to target extra-skeletal effects.[18] Vitamin D binding protein (VDBP) binds up to 90% of serum 25(OH)D, varies with race, and may impact bioavailability of vitamin D metabolites, but its potential effect on treatment response is not known.[1,19-21]

Supported by limited clinical trial evidence,[16,22] the Endocrine Society recommends 6 weeks of treatment with either ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) at doses of 50 000 IU/wk or 2000 IU/d for vitamin D deficiency in infants, children, and adolescents aged 1-18 years.[17] For adults, the recommendation is 8 weeks of 50 000 IU/wk or 6000 IU/d to treat vitamin D deficiency.[17] In these guidelines, the Endocrine Society acknowledges that clinical trials are needed to better inform these recommendations

25(OH)D	25-hydroxyvitamin D
BMI	Body mass index
Cholecalciferol	Vitamin D3
Ergocalciferol	Vitamin D2
VDBP	Vitamin D binding protein

across age and weight groups. Indeed, there are few randomized trials of vitamin D supplementation in adolescents[23-25] and even fewer trials of treatment of vitamin D deficiency in US adolescents.[26,27] These trials find dose-dependent and duration of treatment-dependent responses when comparing doses ranging from 200-4000 IU/d for 4 weeks up to 1 year. For vitamin D-deficient adults, a 6-month, randomized controlled treatment trial calculated that a dose of 5000 IU/d of vitamin D3 was needed to raise 25(OH)D levels to sufficiency.[15] A 2012 meta-analysis suggests that vitamin D3 is more potent and better stored by the body than vitamin D2.[28]

In this trial, we compared vitamin D3 treatment regimens in vitamin D-deficient, predominantly Hispanic and black adolescents living in Bronx, New York (latitude 40.8° NE), known for its diverse population and high rates of asthma, obesity, diabetes, and cardiovascular disease.[29,30] We explored factors that may impact treatment efficacy including obesity, skin pigmentation, VDBP levels, and severity of vitamin D deficiency.

Methods

This study was a prospective, open label, randomized clinical trial of 3, 8-week, vitamin D3 treatment regimens in adolescents identified with vitamin D deficiency. We compared 2 high-dose regimens (50 000 IU/wk and 5000 IU/d) and 1 low-dose regimen (1000 IU/d). Recognizing that adolescents are adult-sized, we chose the doses and treatment duration based on recommendations for adults rather than for children. Our low-dose regimen was similar to supplemental dosing recommended for adults. The study was approved by the Institutional Review Board of the Albert Einstein College of Medicine/Children's Hospital at Montefiore.

We recruited patients aged 13-20 years from the Adolescent Medicine and Pediatric Endocrinology practices at Children's Hospital at Montefiore. Exclusion criteria included currently receiving treatment for vitamin D deficiency, hepatic or renal disease, metabolic rickets, and inability to complete the questionnaire. Informed consent was obtained from participants aged 18 years and older and from parents of those younger than 18, from whom assent was also obtained. Of 503 consecutive patients approached, 305 met eligibility criteria and consented to screening (Figure 1; available at www.jpeds.com). Of the 305 adolescents screened, 203 (66%) were vitamin D deficient: 25(OH)D <20 ng/mL, and 81 (27%) were vitamin D insufficient: 25(OH)D 20-30 ng/mL. Of the 203 adolescents identified with vitamin D deficiency, we were unable to further contact 20. Thus, 183 participants with a mean age of 16.6 ± 2.2 years constitute the sample for this trial. Eighty-eight percent identified as either Hispanic or black; 35% were obese (body mass index [BMI]% >95th percentile for age and sex); 63% had at least 1 of 4 chronic conditions, (asthma, diabetes, polycystic ovary syndrome, and hypertension) (Table I).

Participants were randomized to 1 of 3 treatment arms using computer generated randomization. Randomization was based on a permuted block design in sequences of 9 to ensure a fair distribution across the year-long enrollment period and the sequence was concealed. The correct dose and number of capsules of vitamin D3 needed for each arm of the 8-week

Table I. Comparison of baseline characteristics of participants by treatment arm

	Total N = 183	Arm 1 50 000 IU/wk N = 59	Arm 2 5000 IU/d N = 63	Arm 3 1000 IU/d N = 61	P*
Mean serum 25(OH)D ng/mL	13.7 ± 3.9	13.9 ± 3.7	13.4 ± 3.7	13.9 ± 4.2	.75
Mean age, y	16.6 ± 2.2	16.5 ± 2.4	16.6 ± 2.1	16.8 ± 2.1	.81
Sex (%)					
Female	74	75	73	74	
Male	26	25	27	26	.98
Race/ethnicity (%)					
Hispanic	58	66	51	59	
Black	30	25	33	30	
White/Asian/other	12	10	13	13	.43
Skin phototype (%)					
I-II (burn easily)	5	5	3	6	
III (burn moderately)	30	29	24	36	
IV-VI (burn rarely)	65	66	73	57	.86
Mean BMI, kg/m^2	27.8 ± 8.8	28.8 ± 10.4	28.0 ± 8.5	26.9 ± 7.2	.55
Obese (BMI% >95th percentile for age and sex) (%)	35	36	38	32	.71
Season of enrollment (%)					
Winter	33	36	30	34	
Spring	26	24	30	23	
Summer	20	24	16	21	
Fall	21	17	24	21	.84
Sun exposure >2 h/d (%)	45	42	47	44	.83
Sunscreen, past 3 mo (%)	28	22	24	39	.07
Vitamin D deficiency, history of (%)	27	22	25	33	.39
Chronic condition† (%)	63	66	60	64	.79

*From Pearson χ^2, Fisher exact test, or ANOVA, as appropriate for distribution of the variable. P values are provided for convenience to assess balance of potential confounders, knowing that as randomized groups, the participants in the 3 arms came from the same population.
†Asthma; diabetes; hypertension; polycystic ovary syndrome.

treatment course was prepared by the research pharmacy and dispensed by a physician investigator. Vitamin D3 medications were donated by Bio-Tech Pharmacal, Inc (Fayetteville, Arkansas) and provided at no cost to participants. Neither participants nor investigators were blinded to treatment assignments. During the final week of treatment, participants were contacted by telephone to complete an adherence survey and to schedule a posttreatment visit within 2-4 weeks; a gift card ($10 value) was offered as incentive. A total of 122 participants (67%) completed the posttreatment measures and are analyzed for the complete-case analysis (Figure 1). We compared those lost to follow-up (n = 61) with those who completed posttreatment measures (n = 122) and found no difference in age, sex, ethnicity, baseline serum 25(OH)D level, BMI, or season of enrollment.

Measures

The questionnaire and clinical data were completed at enrollment. Laboratory assessments were performed at enrollment and posttreatment. Participants completed a self-administered questionnaire asking about demographics; sunlight exposure; past history of vitamin D deficiency; and illness history. Total serum 25(OH)D level (vitamin D2 plus vitamin D3) was measured using chemiluminescence assay (Diasorin, Inc, Stillwater, Minnesota) at the Moses Special Endocrinology laboratory at Montefiore Medical Center (average coefficient of variance 2.5%). Serum VDBP level was measured using the quantikine human VDBP immunoassay (R and D Systems, Minneapolis, Minnesota) at the Biomarker Analytic Research Core Laboratory at Albert Einstein College of Medicine. VDBP assays were run in duplicate with the average being reported (average coefficient of variance 2.2%). Weight, height, and BMI were obtained from the medical record on the date of enrollment and BMI percentiles for age and sex were calculated. Skin phototype was measured by participant report of their skin color match to a Fitzpatrick Skin Phototype Classification chart, ranging from type I (burn always) to type VI (never burn).[31] We designated season of enrollment as winter (December 22-March 21); spring (March 22-June 21); summer (June 22-September 21); and fall (September 22-December 21). We calculated adherence as the percentage of prescribed doses taken based on a participant survey during the final week of treatment.

Analyses

Power calculation for our primary outcome variable, change in serum 25(OH)D level, indicated that 32 subjects per arm would provide 80% power to detect a difference of 5 ng/mL with 2-tailed alpha of 0.05. Bivariate analyses using χ^2, Student t test, ANOVA, Spearman and Pearson correlation, as appropriate, were performed to compare change in serum 25(OH)D level after treatment and to examine associations with variables of interest. For analysis, obesity was defined as BMI% >95th percentile for age and sex, normal weight as BMI% <85th percentile for age and sex; severe vitamin D deficiency as 25(OH)D <10 ng/mL; and mild/moderate

deficiency as 25(OH)D 10-20 ng/mL. Serum VDBP had a bimodal distribution. For analysis, we dichotomized VDBP levels into 2 groups: high and low, at the midpoint of the 2 peaks (160 µg/mL). In addition to the complete-case analysis reported here, using Stata's multiple imputation procedure we performed an intention-to-treat analysis with 40 imputations (M = 40, rseed 2232). We examined the independent associations of age, sex, ethnicity, weight status, degree of deficiency and adherence with change in 25(OH)D level using multiple linear regression. All analyses were carried out using Stata v 13.0 (Stata, College Station, Texas) with a 2-sided alpha of .05 to denote significance.

Results

Patients were recruited from February 2013-February 2014. The mean baseline serum 25(OH)D level was 13.7 ± 3.9 ng/mL with no meaningful difference among the 3 treatment arms. In addition, there were no meaningful differences in demographic or clinical characteristics among the 3 arms (Table I).

Comparison of Treatment Response by Treatment Arm

The mean change in serum 25(OH)D level, the primary outcome variable for this trial, was significantly different (P < .001) among the 3 treatment arms, with the low-dose arm, as expected, showing the least change (smallest increase) in 25(OH)D level (Table II). The mean change in 25(OH)D level between the 2 high-dose arms, weekly vs daily, was not significantly different (P = .98), despite the total dose of vitamin D3 in the 5000 IU/d arm being only 70% of that in the 50 000 IU/wk arm. Both high-dose treatments were effective in increasing the 25(OH)D level out of the deficiency range (≥20 ng/mL) in more than 80% of participants. The proportion of participants achieving vitamin D sufficiency in the 2 high-dose arms was not statistically different (72% with the weekly dose vs 56% with the daily dose, P = .18). The highest posttreatment 25(OH)D level was 66.5 ng/mL, well below toxic range (88-100 ng/mL).[32] The mean baseline VDBP level was almost twice as high in the 66 Hispanic participants compared with the 34 black participants (P < .001) and did not change with vitamin D3 treatment (Table II). The mean posttreatment serum 25(OH)D level in each of the high-dose arms was in the sufficient range, whereas, the mean posttreatment level in the low-dose arm remained in the deficient range (Figure 2, A).

Factors Associated with Treatment Response

Overall, obese participants (BMI% >95th percentile for age and sex [N = 40]) had little more than one-half the mean change in 25(OH)D level after treatment compared with normal-weight participants (BMI% <85th percentile for age and sex [N = 63]), 13.7 ± 10.7 vs 21.9 ± 16.9 ng/mL, respectively, P < .001. We found differences in the pattern of treatment response within vitamin D3 treatment arms

Table II. Comparison of treatment response and factors that impact efficacy by treatment arm

	Total N = 122	Arm 1 50 000 IU/wk N = 39	Arm 2 5000 IU/d N = 41	Arm 3 1000 IU/d N = 42	P*
Mean serum 25(OH)D (ng/mL)					
Baseline	13.5 ± 3.9	14.0 ± 3.7	13.0 ± 3.9	13.6 ± 4.1	.79
Posttreatment	30.7 ± 14.7	39.0 ± 15.1	34.0 ± 14.3	19.8 ± 5.3	<.001
Change	17.2 ± 15.1	24.9 ± 15.1	21.0 ± 15.2	6.2 ± 6.5	<.001
Posttreatment category (%)					
Deficient	28	5	17	60	
Insufficient	30	23	27	38	
Sufficient	43	72	56	2	<.001
Obese (BMI% >95th percentile for age and sex) (%)	33	33	34	31	.71
Severe deficiency: 25(OH)D <10 ng/mL (%)	20	15	22	21	.92
Adherence (%)	76	80	75	73	.68
Highest 25(OH)D ng/mL	66.5	66.5	66.3	30.4	<.001
Mean serum VDBP (μg/mL)					
Baseline	180.5 ± 110	175.9 ± 111.1	174.7 ± 119.8	190.6 ± 100.2	.54
Posttreatment	173.7 ± 106	158 ± 80.7	163 ± 118	200.2 ± 114.5	.16
Hispanic participants	N = 66	N = 25	N = 20	N = 21	
Mean serum VDBP (μg/mL)					
Baseline	211.3 ± 113.1	200.7 ± 117	212.8 ± 115.0	222.4 ± 110.3	.81
Posttreatment	200.2 ± 106	178.8 ± 77.7	200.6 ± 115	226.5 ± 12.3	.70
Black participants	N = 34	N = 9	N = 12	N = 13	
Mean serum VDBP (μg/mL)					
Baseline	113.4 ± 61.2	122.5 ± 76	89.0 ± 46	129.0 ± 59.3	.11
Posttreatment	113.0 ± 68.0	108.1 ± 76	92.0 ± 49.1	136.5 ± 76.0	.33

*From ANOVA, Pearson χ^2, or Kruskal-Wallis test, as appropriate for distribution of the variable.

when comparing obese and normal-weight participants (**Figure 2**, B). Within the low-dose arm, there was no meaningful difference in treatment response between weight groups, however, obese participants who received the daily high-dose treatment had a significantly lower treatment response than normal-weight participants. The difference in treatment response in the weekly high-dose arm was in the same direction but not statistically
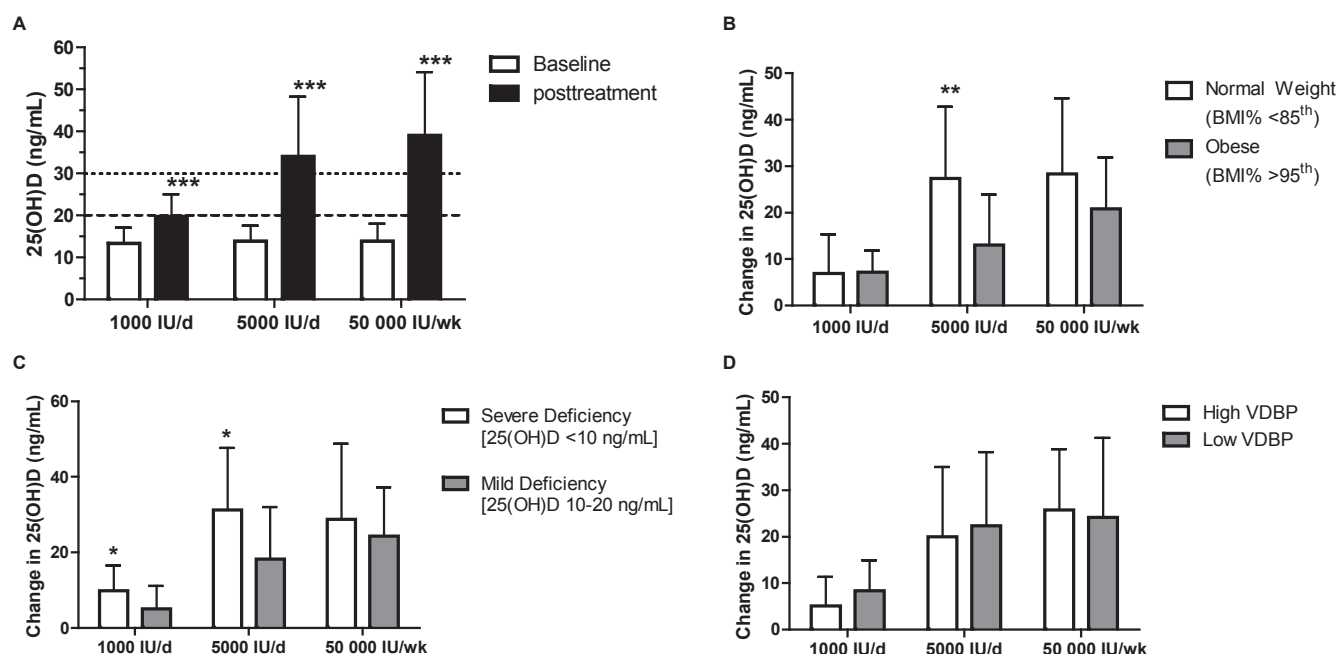

Figure 2. A, Comparison of mean 25(OH)D level pre- and posttreatment. *Dashed line* indicates vitamin D deficiency and *dotted line* indicates sufficiency. **B,** Comparison of change in 25(OH)D level after treatment for normal weight vs obese participants. **C,** Comparison of change in 25(OH)D level after treatment for participants with severe deficiency vs mild deficiency. **D,** Comparison of change in 25(OH)D level after treatment for participants with high VDBP level vs low VDBP level. Error bars show SD. *P < .05; **P < .01; ***P < .001.

significant. For normal-weight participants mean change in 25(OH)D level with the 2 high-dose regimens was similar, weekly vs daily, (28.3 ± 16.3 vs 27.4 ± 15.4 ng/mL, respectively, $P = .79$). For obese participants the higher total dose in the weekly regimen resulted in an apparent greater increase in 25(OH)D level vs the 30% lower dose in the 5000 IU/d regimen (20.8 ± 11.1 vs 13.1 ± 10.8 ng/mL, respectively, $P = .08$), although this difference did not reach statistical significance.

For the total sample, comparison of the 24 participants with severe vitamin D deficiency: 25(OH)D <10 ng/mL to the 98 with mild/moderate deficiency indicated a significantly greater increase in 25(OH)D level after treatment in the severely deficient participants (22.6 ± 18.6 vs 15.8 ± 13.9 ng/mL, respectively, $P = .04$). Comparison of severe vs mild/moderate deficiency within each of the 3 treatment arms is shown in Figure 2, C.

Comparison of the 70 participants with High VDBP levels to the 52 with Low VDBP levels indicated that the mean change in 25(OH)D level after treatment was similar (15.6 ± 14.5 vs 19.3 ± 15.7 ng/mL, respectively, $P = .18$) and comparison within treatment arms also showed no difference (Figure 2, D). VDBP level was not significantly correlated with treatment response within the Hispanic (Spearman rho = −0.01, $P = .91$) or black (Spearman rho = −0.17, $P = .35$) groups. In addition, we found no significant difference in treatment response by race/ethnicity, age, sex, or skin phototype. As expected, percent adherence was positively and significantly correlated with mean change in serum 25(OH)D level (Pearson r = 0.25, $P = .01$).

Regression Model of Independent Associations with Treatment Response

We show a model that explained 46% of the variability in treatment response, with each of the covariables: high-dose treatment arms 1 and 2; obese weight status; severe vitamin D deficiency; and adherence showing an independent association with change in 25(OH)D after treatment (Table III; available at www.jpeds.com).

For the intent-to-treat analysis, our imputation model included age, sex, ethnicity, baseline 25(OH)D level, BMI percentile, season of enrollment, and study arm. The results of a regression using the multiple imputed values yielded the same P value for comparison by treatment arm ($P < .001$) as that of the complete-case analysis when comparing on our primary outcome variable, change in serum 25(OH)D.

Discussion

In this 8-week trial of treatment of vitamin D deficiency in predominantly Hispanic and black adolescents, we found that the response to a weekly vitamin D3 regimen of 50 000 IU was comparable with a daily regimen of 5000 IU in raising levels of 25(OH)D out of the deficient range (≥20 ng/mL). A daily regimen of 1000 IU was much less effective. Although

we treated our participants with a higher daily dose and longer treatment duration than recommended for children aged 1-18 years by the Endocrine Society, none of our participants achieved 25(OH)D levels approaching the toxic range. Indeed, after 8 weeks of treatment only 72% and 56% of adolescents treated with the weekly and daily high-dose regimens achieved vitamin D sufficiency. Participants randomized to the daily low-dose (1000 IU) regimen had lower treatment responses similar to those found in adults receiving the same dose.[33] Weight-based dosing is a canon of pediatric pharmacology, and it is not surprising that our adult-sized adolescents benefited from doses and duration of treatment based on adult treatment recommendations. A meta-analysis for rapid normalization of vitamin D levels (within 1 month) in pediatric trials found greater efficacy for single or intermittent high-dose loading regimens (≥50 000 IU) compared with daily low-dose regimens (1000-4000 IU) in children and called for more trials studying loading-dose regimens, especially in adolescent patients.[32] Further, they reported an adverse event analysis showing the safety of doses <400 000 IU in adolescents.

Although a treatment trial of vitamin D deficient infants and toddlers[16] showed no difference in outcome when comparing 6-weeks of treatment with 2000 IU/d of vitamin D2 or D3 and 50 000 IU/wk of vitamin D2, we found that, for our adolescent participants, high-dose vitamin D3 produced a superior treatment response when compared with low-dose treatment. A trial in 336 vitamin D-deficient Lebanese adolescents using 2000 IU/d of vitamin D3 found that 64% achieved sufficiency, 25(OH)D ≥30 ng/mL, after 1 year.[34] Importantly, a similar proportion of our participants in the high-dose treatment arms achieved sufficiency after only 8 weeks. If rapid normalization of 25(OH)D levels is the treatment goal as is likely for studies of extra-skeletal health outcomes, higher doses of vitamin D3 are more effective at achieving this goal.

Our multivariable analysis indicated that obesity and severe deficiency were independent predictors of treatment response, with obese adolescents having a poorer response and adolescents with severe deficiency having a better response than the sample as a whole. Levels of 25(OH)D are lower in obese individuals, thought to be from sequestration in body fat or volume dilution, and the optimal dosing regimen for obese, vitamin D-deficient adolescents is not clear.[19,35] We found no other trials in vitamin D-deficient adolescents comparing treatment response by weight status. However, a study of black adolescents showed a negative correlation of treatment response with adiposity measured by dual-energy x-ray absorptiometry.[26] Two small vitamin D3 trials in obese youth using 4000 IU/d for 12-24 weeks and 50 000 IU/wk for 8 weeks had treatment responses approximating those in the obese participants in our trial.[5,8] A 21-week trial in adults quantified the dose of D3 needed to raise the 25(OH)D level based on the individual's weight and found that obese adults had about a 30% lower response to the same dose of vitamin D as the nonobese.[36] The investigators concluded

that obese individuals need higher doses of vitamin D3 than nonobese individuals to attain the same increment of 25(OH)D. Similarly in our trial, we found the mean increase in 25(OH)D level after treatment was nearly 40% less in obese than in normal-weight participants. Whereas for our normal-weight participants response to both 8-week, high-dose treatment regimens was comparable, obese participants had a better response with the higher cumulative dose (400 000 IU) in the weekly regimen vs the lower dose (280 000 IU) in the daily regimen. We caution that our within treatment group analyses are exploratory, but they raise important considerations in determining the ideal dosing for obese adolescents. Evidence from dose response curves in obese and nonobese adults suggests that volume dilution rather than sequestration in fat accounts for the differences in treatment response.[37] We have no reason to believe that vitamin D is metabolized differently in obese adolescents than in obese adults and suggest that weight-based dosing should be investigated further to establish a standard for treatment of vitamin D-deficient adolescents. Our trial, like the adult trial, suggests that vitamin D-deficient obese adolescents may benefit from higher doses of vitamin D3 than normal-weight adolescents.

Other treatment trials in adolescents have reported a negative correlation of baseline 25(OH)D levels and treatment response.[32,34] In this study, we further categorize severe and mild/moderate vitamin D deficiency to inform treatment decisions in clinical practice. Our study suggests that adolescents with severe deficiency do not necessarily need higher treatment doses than those with milder deficiency as they have better treatment responses.

Two studies report that white adults have double the VDBP levels compared with black adults.[21,38] Similar to white adults, our Hispanic participants had VDBP levels approximately double the levels in black participants. Of note, controversy exists surrounding the use of a monoclonal VDBP immunoassay in that racial/ethnic differences may reflect different affinities of proteins by varying genotypes. The issue is potentially of importance, as blacks seem to have higher levels of an isoform not detected by the assay, which could also account for the lower levels of VDBP that we found in black as compared with Hispanic participants. This debate is addressed in recent published correspondence and studies clarifying the measurement of VDBP as well as free or bioavailable vitamin D are forthcoming.[39,40] A novel finding of this study of Hispanic and black adolescents is that VDBP levels did not change with vitamin D3 treatment, indicating that vitamin D may not directly regulate VDBP levels. Conversely, baseline VDBP levels did not affect response to D3 treatment in any of our treatment arms. Although one might expect VDBP levels may alter the pharmacokinetics of vitamin D, levels have been shown to be independent of the effect of vitamin D on parathyroid hormone and calcium.[21] On the other hand, recent findings that genetic variation in the VDBP gene, *Gc*, is associated with serum 25(OH)D levels and influences responsiveness

to vitamin D3 supplementation indicates that further research in this area is needed.[41,42]

Limitations of this study include a substantial attrition rate, although our multiple imputation analysis suggests that the complete-case analysis reported here was essentially the same as an intention-to-treat analysis, and we have no reason to believe that the missing at random assumption does not hold. In addition, our trial was not powered for the within treatment arm, subgroup analyses, and these findings must be interpreted with caution. ∎

References

1. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
2. Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. BMJ 2014;348: g2035.
3. Sonneville KR, Gordon CM, Kocher MS, Pierce LM, Ramappa A, Field AE. Vitamin d, calcium, and dairy intakes and stress fractures among female adolescents. Arch Pediatr Adolesc Med 2012;166:595-600.
4. Winzenberg T, Powell S, Shaw KA, Jones G. Effects of vitamin D supplementation on bone density in healthy children: systematic review and meta-analysis. BMJ 2011;342:c7254.
5. Ashraf AP, Alvarez JA, Gower BA, Saenz KH, McCormick KL. Associations of serum 25-hydroxyvitamin D and components of the metabolic syndrome in obese adolescent females. Obesity (Silver Spring) 2011;19: 2214-21.
6. Reis JP, von Muhlen D, Miller ER III, Michos ED, Appel LJ. Vitamin D status and cardiometabolic risk factors in the United States adolescent population. Pediatrics 2009;124:e371-9.
7. Dolinsky DH, Armstrong S, Mangarelli C, Kemper AR. The association between vitamin D and cardiometabolic risk factors in children: a systematic review. Clin Pediatr (Phila) 2013;52:210-23.
8. Belenchia AM, Tosh AK, Hillman LS, Peterson CA. Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial. Am J Clin Nutr 2013;97:774-81.
9. Raja-Khan N, Shah J, Stetter CM, Lott ME, Kunselman AR, Dodson WC, et al. High-dose vitamin D supplementation and measures of insulin sensitivity in polycystic ovary syndrome: a randomized, controlled pilot trial. Fertil Steril 2014;101:1740-6.
10. Kelishadi R, Salek S, Salek M, Hashemipour M, Movahedian M. Effects of vitamin D supplementation on insulin resistance and cardiometabolic risk factors in children with metabolic syndrome: a triple-masked controlled trial. J Pediatr (Rio J) 2014;90:28-34.
11. Dong Y, Pollock N, Stallmann-Jorgensen IS, Gutin B, Lan L, Chen TC, et al. Low 25-hydroxyvitamin D levels in adolescents: race, season, adiposity, physical activity, and fitness. Pediatrics 2010;125:1104-11.

12. Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. Arch Intern Med 2009;169:626-32.

13. Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001-2004. Pediatrics 2009;124:e362-70.

14. Turer CB, Lin H, Flores G. Prevalence of vitamin D deficiency among overweight and obese US children. Pediatrics 2013;131:e152-61.

15. Aloia JF, Patel M, Dimaano R, Li-Ng M, Talwar SA, Mikhail M, et al. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. Am J Clin Nutr 2008;87:1952-8.

16. Gordon CM, Williams AL, Feldman HA, May J, Sinclair L, Vasquez A, et al. Treatment of hypovitaminosis D in infants and toddlers. J Clin Endocrinol Metab 2008;93:2716-21.

17. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-30.

18. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. J Clin Endocrinol Metab 2012;97:1153-8.

19. Ashraf AP, Huisingh C, Alvarez JA, Wang X, Gower BA. Insulin resistance indices are inversely associated with vitamin D binding protein concentrations. J Clin Endocrinol Metab 2014;99:178-83.

20. Carpenter TO, Zhang JH, Parra E, Ellis BK, Simpson C, Lee WM, et al. Vitamin D binding protein is a key determinant of 25-hydroxyvitamin D levels in infants and toddlers. J Bone Miner Res 2013;28:213-21.

21. Ponda MP, McGee D, Breslow JL. Vitamin D-binding protein levels do not influence the effect of vitamin D repletion on serum PTH and calcium: data from a randomized, controlled trial. J Clin Endocrinol Metab 2014;99:2494-9.

22. Maalouf J, Nabulsi M, Vieth R, Kimball S, El-Rassi R, Mahfoud Z, et al. Short- and long-term safety of weekly high-dose vitamin D3 supplementation in school children. J Clin Endocrinol Metab 2008;93:2693-701.

23. Lewis RD, Laing EM, Hill Gallant KM, Hall DB, McCabe GP, Hausman DB, et al. A randomized trial of vitamin D(3) supplementation in children: dose-response effects on vitamin D metabolites and calcium absorption. J Clin Endocrinol Metab 2013;98:4816-25.

24. Putman MS, Pitts SA, Milliren CE, Feldman HA, Reinold K, Gordon CM. A randomized clinical trial of vitamin D supplementation in healthy adolescents. J Adolesc Health 2013;52:592-8.

25. Rajakumar K, Moore CG, Yabes J, Olabopo F, Haralam MA, Comer D, et al. Effect of vitamin D3 supplementation in black and in white children: a randomized, placebo-controlled trial. J Clin Endocrinol Metab 2015;100:3183-92.

26. Dong Y, Stallmann-Jorgensen IS, Pollock NK, Harris RA, Keeton D, Huang Y, et al. A 16-week randomized clinical trial of 2000 international units daily vitamin D3 supplementation in black youth: 25-hydroxyvitamin D, adiposity, and arterial stiffness. J Clin Endocrinol Metab 2010;95:4584-91.

27. Pappa HM, Mitchell PD, Jiang H, Kassiff S, Filip-Dhima R, DiFabio D, et al. Treatment of vitamin D insufficiency in children and adolescents with inflammatory bowel disease: a randomized clinical trial comparing three regimens. J Clin Endocrinol Metab 2012;97:2134-42.

28. Tripkovic L, Lambert H, Hart K, Smith CP, Bucca G, Penson S, et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. Am J Clin Nutr 2012;95:1357-64.

29. United States Census Bureau: State and County Quickfacts [updated 2015 May 29]. quickfacts.census.gov/qfd/states/36/36005.html. Accessed June 1, 2015.

30. New York State Department of Health: Bronx County Indicators For Tracking Public Health Priority Areas [updated 2012 Oct]. http://www.health.ny.gov/prevention/prevention_agenda/indicators/county/bronx.html. Accessed May 5, 2015.

31. Magin P, Pond D, Smith W, Goode S, Paterson N. Reliability of skin-type self-assessment: agreement of adolescents' repeated Fitzpatrick skin phototype classification ratings during a cohort study. J Eur Acad Dermatol Venereol 2011;11:1396-9.

32. McNally JD, Iliriani K, Pojsupap S, Sampson M, O'Hearn K, McIntyre L, et al. Rapid normalization of vitamin D levels: a meta-analysis. Pediatrics 2015;135:e152-66.

33. Holick MF, Biancuzzo RM, Chen TC, Klein EK, Young A, Bibuld D, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. J Clin Endocrinol Metab 2008;93:677-81.

34. Al-Shaar L, Mneimneh R, Nabulsi, Maalouf J, Fuleihan Gel H. Vitamin D3 dose requirement to raise 25-hydroxyvitamin D to desirable levels in adolescents: results from a randomized controlled trial. J Bone Miner Res 2014;29:944-51.

35. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72:690-3.

36. Drincic A, Fuller E, Heaney RP, Armas LA. 25-Hydroxyvitamin D response to graded vitamin D(3) supplementation among obese adults. J Clin Endocrinol Metab 2013;98:4845-51.

37. Drincic AT, Armas LA, Van Diest EE, Heaney RP. Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. Obesity (Silver Spring) 2012;20:1444-8.

38. Powe CE, Evans MK, Wenger J, Zonderman AB, Berg AH, Nalls M, et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. N Engl J Med 2013;369:1991-2000.

39. Chen Y. Vitamin D-binding protein and vitamin D in blacks and whites. N Engl J Med 2014;370:878-9.

40. Aloia J, Mikhail M, Dhaliwal R, Shieh A, Usera G, Stolberg A, et al. Free 25(OH)D and the vitamin D paradox in African Americans. J Clin Endocrinol Metab 2015;100:3356-63.

41. Fu L, Yun F, Oczak M, Wong BY, Vieth R, Cole DE. Common genetic variants of the vitamin D binding protein (DBP) predict differences in response of serum 25-hydroxyvitamin D [25(OH)D] to vitamin D supplementation. Clin Biochem 2009;42:1174-7.

42. Nimitphong H, Saetung S, Chanprasertyotin S, Chailurkit LO, Ongphiphadhanakul B. Changes in circulating 25-hydroxyvitamin D according to vitamin D binding protein genotypes after vitamin D(3) or D(2)supplementation. Nutr J 2013;12:39.
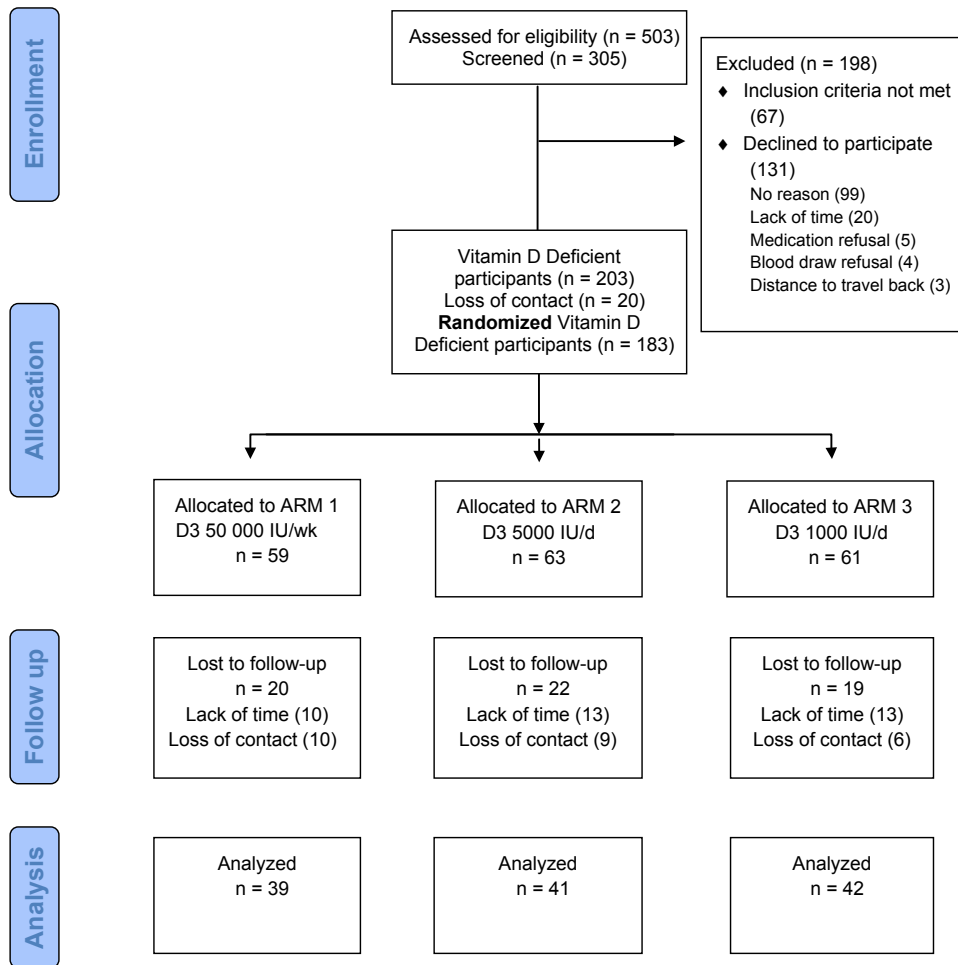
Figure 1. CONSORT flowchart showing the progress of participants through each stage of this randomized clinical trial.

Table III. Multiple linear regression of variables affecting change in serum 25(OH)D

Variables	Coefficients (95% CI)	P
Study arm 1 (50 000 IU/wk)	19.7 (13.3, 26.2)	<.001
Study arm 2 (5000 IU/d)	16.7 (10.3, 23.2)	<.001
Adherence%	0.13 (0.01, 0.27)	.04
Severe vitamin D deficiency	−9.5 (−12.0, −1.4)	.005
Obese weight status	−6.7 (−0.19, −0.04)	.01

$P < .001$; $R^2 = 0.46$, adjusted $R^2 = 0.43$.