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 (≥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.

Vitamin 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

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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.