Journal of Adolescent Health 57 (2015) 19–23

ELSEVIER

JOURNAL OF ADOLESCENT HEALTH

www.jahonline.org

Original article

Large Doses of Vitamin D Fail to Increase 25-Hydroxyvitamin D Levels or to Alter Cardiovascular Risk Factors in Obese Adolescents: A Pilot Study

Sejal Shah, M.D. *, Darrell M. Wilson, M.D., and Laura K. Bachrach, M.D.

Division of Pediatric Endocrinology and Diabetes, Stanford University, Stanford, California

Article history: Received October 30, 2014; Accepted February 1, 2015
Keywords: Vitamin D supplementation; Obesity; Adolescents; Randomized controlled trial; Inflammation; Cytokines; Cardiovascular risk factors

See Related Editorial p. 1

A B S T R A C T

Purpose: Vitamin D deficiency and cardiometabolic risk factors are common in obese adolescents. Observational studies demonstrate an inverse relationship among serum 25-hydroxyvitamin D (25OHD) and obesity, insulin resistance, and inflammatory cytokines. This pilot study explores if vitamin D supplementation could reduce serum concentrations of inflammatory cytokines (interleukin [IL] 6, IL-10, tumor necrosis factor α), adiponectin, lipids, hemoglobin A1C, and high-sensitivity C-reactive protein (hs-CRP). A secondary aim was to determine the associations between baseline serum 25OHD concentrations and body mass index (BMI), hs-CRP, inflammatory cytokines, and lipids.
Methods: Overweight and obese adolescents enrolled in this 24-week, randomized, double-blind study were given 150,000 IU ergocalciferol or placebo at baseline and 12 weeks. Outcome measurements included serum 25OHD, inflammatory cytokines, adiponectin, hs-CRP, lipids, hemoglobin A1C, and BMI at baseline, 12, and 24 weeks.
Results: Of 40 participants, 31 (78%) completed the study. Mean ± standard error 25OHD levels were similar in vitamin D and placebo groups at baseline (19.6 ± 5.3 vs. 25.8 ± 10.8 ng/mL) and 24 weeks (20.1 ± 3.4 vs. 24.6 ± 8.4 ng/mL). Inflammatory and cardiovascular markers were not significantly different between groups at 24 weeks. Serum 25OHD at baseline was associated with BMI ($r = -.44$ [95% confidence interval, −.66 to −.15]) but not with other outcome measures.
Conclusions: Supplementation with vitamin D at 150,000 IU every 3 months failed to increase serum 25OHD or alter inflammatory markers and lipids in overweight and obese youth. Further studies are needed to establish the dose of vitamin D required to increase 25OHD and determine potential effects on metabolic risk factors in obese teens.

IMPLICATIONS AND CONTRIBUTION

Supplementation with 150,000 IU of ergocalciferol every 3 months failed to increase serum 25OHD in obese adolescents or to alter biochemical inflammatory or metabolic markers. Determining if vitamin D supplementation can impact obesity-related complications is critical given the alarming rates of obesity and metabolic syndrome among adolescents.

The epidemic of obesity and metabolic syndrome among children and adolescents is alarming, with 35% of U.S. children aged 6–19 years defined as obese [1]. A healthy diet and increased activity are first steps toward preventing and reducing obesity-related complications, but interest in adjunct therapies is growing. Vitamin D has been identified as a potential therapy

Conflicts of Interest: The authors declare no potential conflicts of interest, real or perceived.
ClinicalTrials.gov Identifier: NCT01217840.

* Address correspondence to: Sejal Shah, M.D., Division of Pediatric Endocrinology and Diabetes, Stanford University, 300 Pasteur Drive, G-313, Stanford, CA 94305.
E-mail address: sshah2@stanford.edu (S. Shah).

1054-139X/
http://dx.doi.org/10.1016/j.jadohealth.2015.02.006

based on the observation that circulating 25-hydroxyvitamin D (25OHD) is inversely correlated to body mass index (BMI), hypertension, inflammatory markers, and insulin resistance in children [2–5] and adults [6,7]. Without studies of vitamin D supplementation, however, it is unclear whether low vitamin D is only associated with these metabolic risk factors or causal.

The prevalence of vitamin D deficiency (defined in this article as 25OHD $\leq$ 20 ng/mL) is 29% and 35% in overweight and obese children aged 6–18 years, respectively, with higher rates in minority children [8]. Obesity is associated with higher levels of inflammatory markers (high-sensitivity C-reactive protein [hs-CRP], interleukin [IL] 6, and tumor necrosis factor α [TNF-α]), and lower levels of adiponectin [9,10]. This chronic inflammatory state is linked to decreased insulin sensitivity and other consequences of the metabolic syndrome. Whether vitamin D supplementation can alter these associations has been examined in short-term trials of obese adolescents. Supplementation with 2000 IU of cholecalciferol daily improved arterial stiffness [11], but daily supplementation with 2000 or 4000 IU daily of cholecalciferol yielded inconsistent effects on insulin sensitivity [12,13].

This randomized, placebo-controlled pilot study was designed to examine the effects of 6 months of supplemental vitamin D2 (150,000 IU every 12 weeks, equivalent to 1780 IU/day) on serum 25OHD concentrations and markers of inflammation and hemoglobin A1C in overweight and obese adolescents. We hypothesized that vitamin D supplementation would increase serum 25OHD concentrations and reduce inflammatory cytokines and markers of cardiometabolic risk.

Methods

Subjects

Subjects were recruited from the pediatric endocrinology, weight, and primary care clinics at Lucile Packard Children's Hospital at Stanford University and affiliated clinics (Stanford, CA, latitude 37° N). Inclusion criteria included ages 11–17.99 years, BMI of $\geq$85th percentile for age and gender, and serum 25OHD concentration between 10 and 60 ng/mL. Exclusion criteria included medications and supplements (vitamin D $>$ 400 IU/day, glucocorticoids, or antiepileptics), diseases (rickets, diabetes mellitus, liver or kidney disease, and galactosemia), malabsorptive disorders, lactose intolerance, or genetic syndromes associated with obesity. Written informed parental consent and subject assent were obtained before study participation. The protocol was approved by the Stanford University Administrative Panel of Research Involving Human Subjects.

Study design

This study was a 24-week randomized, double-blind, placebo-controlled, single-center clinical trial. Using block randomization with random block size, subjects were assigned to receive two observed doses of vitamin D2 (150,000 IU ergocalciferol, Barr Laboratories and Winthrop [Sanofi-Aventis]) or placebo, given at baseline and 12 weeks [14]. Capsules were packaged by the hospital's clinical trial pharmacist and were administered by study staff blinded to group assignments. Capsules were taken with milk to optimize absorption.

Height, weight, and BMI were obtained at baseline, 12 weeks, and 24 weeks. Fasting morning blood samples were obtained at each visit for measurement of serum 25OHD, intact parathyroid hormone (iPTH), calcium, phosphorus, alkaline phosphatase, glucose, high-density lipoprotein, triglycerides, hs-CRP, IL-6, IL-10, TNF-α, and adiponectin. Serum magnesium and hemoglobin A1C were measured at baseline and 24 weeks. Subjects with serum 25OHD concentration of $<$10 ng/mL at any time point were removed from the study and treated for vitamin D deficiency.

Laboratory assays

Serum total 25OHD was assessed using liquid chromatography–tandem mass spectrometry (AB Sciex). The intra-assay and interassay coefficients of variation were 2%–6% and 8%–12%, respectively. iPTH was measured by chemiluminescent immunometric immunoassay (Immulite 2000, Siemens). hs-CRP was assessed by immunoassay. IL-10, IL-6, and TNF-α were measured by enzyme-linked immunosorbent assay (Meso Scale Discovery, Gaithersburg, MD) in the Human Immune Monitoring Center at Stanford University; results were analyzed with Masterplex software (MiraiBio, San Bruno, CA). Adiponectin was measured by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN). The intra-assay and interassay coefficient of variabilities were 3.5% and 6.5%, respectively. The minimum detectable value is 0.25 ng/mL. To minimize variability in cytokine measurements, serial samples from each subject were batched and analyzed in the same assay.

Statistical analysis and sample size determination

The *t* test was used to compare mean values between groups for each outcome variable at baseline and 24 months. The change in values between groups over the study time period was compared using multivariate analysis of covariance. Associations between 25OHD and outcome variables at baseline were evaluated by Spearman's correlation as the results were not normally distributed. All tests were two sided, and a p value of $<$.05 was considered significant. Statistical analyses were performed using SAS system for Windows, version 9.4 (SAS Institute, Cary, NC) and JMP version 10 (SAS Institute).

The statistical power calculations were based on reported observations of inflammatory cytokines in obese and normal weight youth [9]. A study sample size of 40 subjects (20 per group) would provide an 80% power to detect a delta difference hs-CRP of 0.95 mg/L and a delta difference IL-6 of 0.4 pg/mL in response to vitamin D supplementation.

Results

Subject characteristics

Of the 92 individuals approached who met eligibility criteria, 40 were enrolled between September 2010 and July 2012; 31 (78%) completed the study (Figure 1). The majority of subjects were female and non-white; 48% of subjects had BMI of $>$99% for age and gender (Table 1). At baseline, 50% of subjects were vitamin D deficient (serum 25OHD $<$ 20 ng/mL). Subjects in the vitamin D group were older and had a higher baseline BMI than the placebo group.

Laboratory findings

The mean serum 25OHD concentration was increased by 0.5 ng/mL in the supplemented group and decreased by 1.5 ng/mL in the placebo group between baseline and 24 weeks, a difference that was not significant (Table 2). There was marked

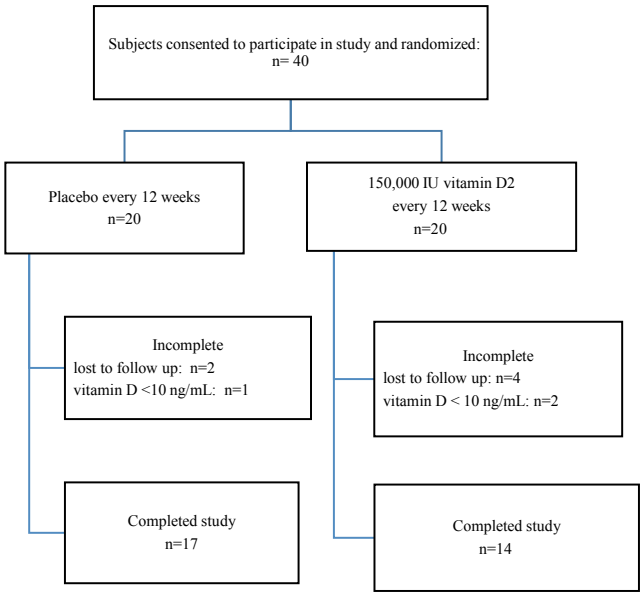

Figure 1. Enrollment, randomization, and follow-up of the study participants.

individual variability in the change in serum 25OHD concentrations (Figure 2).

Serum 25OHD at baseline was inversely associated with BMI ($r = -0.44$ [95% confidence interval, −0.66 to −0.15]) but not with baseline serum concentrations of hs-CRP, lipids, IL-6, IL-10, TNF-α, or adiponectin. Baseline serum metabolic markers and inflammatory makers, with the exception of BMI, were normal for age. There was no significant change in BMI, alkaline phosphatase, iPTH, hs-CRP, lipids, cytokines, or adiponectin after 24 weeks of vitamin D supplementation (Table 2).

Table 1
Clinical characteristics of study participants

	Vitamin D	Placebo
N (male/female)	20 (8/12)	20 (6/14)
Age (year), mean ± SE	15.1 ± 0.4	13.6 ± 0.4[a]
Height (cm), mean ± SE	165.2 ± 2.3	159.5 ± 3
Weight (kg), mean ± SE	99.4 ± 6.2	78.7 ± 4.4
BMI (kg/m^2), mean ± SE	36 ± 1.6	31 ± 1.1[a]
BMI *z* score, mean ± SE	2.30 ± 0.11	1.99 ± .08
Overweight/obese, n	1/19	3/17
Race/ethnicity, n (%)		
White	3 (15)	5 (25)
African American	3 (15)	3 (15)
Hispanic	12 (60)	8 (40)
Asian/Pacific Islander	2 (10)	4 (20)
25OHD (ng/mL), mean ± SE	19.4 ± 1.3	24.2 ± 2.4
Alkaline phosphatase (units/L), mean ± SE	145 ± 14	200 ± 23
iPTH (pg/mL), mean ± SE	46 ± 4	40 ± 5
hs-CRP (mg/L), mean ± SE	4.1 ± 0.7	2 ± 0.5
Triglycerides (mg/dL), mean ± SE	113 ± 15	105 ± 14
HDL (mg/dL), mean ± SE	42 ± 3	46 ± 3
HgbA1C (%), mean ± SE	5.5 ± 0.3	5.3 ± 0.1
IL-6 (pg/mL), median (IQR)	1 (0.8–1.4)	.7 (.4–1.4)
IL-10 (pg/mL), median (IQR)	1.5 (.8–2.3)	1.9 (.7–3.9)
TNF-α (pg/mL), median (IQR)	7.4 (5.8–8.8)	7.2 (6.3–8.4)
Adiponectin (pg/mL), median (IQR)	5.8 (3.6–6.9)	7.1 (3.7–8.8)

25OHD = 25-hydroxyvitamin D; BMI = body mass index; HDL, high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; HgbA1C = hemoglobin A1C; IL = interleukin; iPTH = intact parathyroid hormone; IQR = interquartile range; SE = standard error; TNF-α = tumor necrosis factor α.

[a] $p < .05$.

We did not observe any clinically significant adverse effects during the study. One subject in the placebo group had transient asymptomatic hypercalcemia (10.6 mg/dL) that self-resolved and was not associated with hypervitaminosis D (25OHD, 73 ng/mL).

Discussion

This pilot study was designed to explore if observed supplementation with ergocalciferol would increase serum 25OHD and reduce markers of inflammation and metabolic dysfunction in obese and overweight adolescents. The dose of 150,000 IU given every 12 weeks failed to significantly increase serum 25OHD levels and did not alter serum inflammatory or metabolic markers. This leaves unanswered the question of whether low vitamin D is causally related to metabolic risk factors in obese teens.

The protocol was designed to optimize recruitment, retention, and adherence to medication in an adolescent population. We provided vitamin D supplementation as an observed dose of 150,000 IU every 3 months to ensure adherence. Capsules of ergocalciferol but not cholecalciferol were available in the 50,000 IU dose. Our regimen had been shown in prior studies to increase serum 25OHD from 7.8 to 21.2 ng/mL in postmenarchal females [14]. In another study, an equivalent vitamin D dose (2,000 IU administered daily) increased serum 25OHD concentrations to at least 20 ng/mL in 96% of adolescents [15]. The pediatric literature estimates that serum 25OHD increases by 1 ng/mL for each 100 IU of supplemental vitamin D provided [16,17]. Thus, we anticipated that serum 25OHD might rise by 18 ng/mL with this regimen. Venipuncture was performed only at baseline, 12 weeks, and 24 weeks to coincide with study visits.

There are several potential explanations for the failure of this vitamin D supplementation regimen to increase serum 25OHD. A higher dose of vitamin D may be required to in obese individuals to compensate for sequestration in adipose tissue [18]. One study found that nonobese youth supplemented with 2000 IU/day of vitamin D had a 1.7-fold greater increase in serum 25OHD than did obese youth [19]. Alternatively, supplementation with large doses of ergocalciferol every 3 months may have compromised the response. Daily or weekly supplementation or use of cholecalciferol might have been more effective [20]. Nader et al. [12] demonstrated that supplementation with 2000 IU of cholecalciferol daily for 3 months increased 25OHD by a mean of 5 ng/mL in obese teens. We may have missed the peak concentration of 25OHD by measuring serum only at 12 weeks after each ergocalciferol dose; however, the treatment duration of 6 months appears to be sufficient to evaluate the impact of ergocalciferol supplementation on serum 25OHD concentrations [21]. Other variables that could have influenced the response to vitamin D supplementation include 25-hydroxylase activity and synthesis of vitamin D–binding proteins which we did not assess in our study [22,23]. We did not evaluate the pubertal status of our subjects which may play a role in change in BMI, serum glucose, and lipid levels. Finally, in contrast to the studies by Nader et al. and Belenchia et al., our study population included a majority of nonwhite adolescents whose vitamin D requirements have been less well established [8].

Several factors may also account for the failure to see a change in inflammatory markers in the vitamin D–supplemented group. The intervention did not alter serum 25OHD, an indication of total body stores. Alternatively, it is possible that the effects of supplementation were not seen because our subjects had normal or only mildly deficient

Table 2
Biochemical characteristics of study participants who completed the study

	Baseline		24 weeks	
	Vitamin D, n = 14	Placebo, n = 17	Vitamin D	Placebo
BMI (kg/m^2), mean ± SE	33 ± 1.6	30 ± 1.2	34 ± 1.6	30 ± 1.3
25OHD (ng/mL), mean ± SE	19.6 ± 1.4	25.8 ± 2.6	20.1 ± 0.9	24.6 ± 2
Alkaline phosphatase (units/L), mean ± SE	159 ± 18	202 ± 25	154 ± 22	192 ± 24
iPTH (pg/mL), mean ± SE	44 ± 3	41 ± 5	47 ± 5	37± 4
hs-CRP (mg/L), mean ± SE	4 ± 1	2.2 ± 0.5	4.3 ± 0.9	2.3 ± 0.6
Triglycerides (mg/dL), mean ± SE	106 ± 20	99 ± 13	114 ± 19	99 ± 11
HDL (mg/dL), mean ± SE	41 ± 3	46 ± 3	41 ± 2	47 ± 3
HgbA1C (%), mean ± SE	5.4 ± 0.1	5.3 ± 0.1	5.4 ± 0.1	5.3 ± 0.1
IL-6 (pg/mL), median (IQR)	1 (0.6–1.3)	0.7 (0.4–1.3)	1 (0.7–1.7)	0.7 (0.4–1.2)
IL-10 (pg/mL), median (IQR)	1.7 (0.8–2.2)	2 (0.8–4.6)	1.7 (0.7–4.1)	2.3 (1.2–4.6)
TNF-α (pg/mL), median (IQR)	6 (4.9–8.7)	7.2 (6.4–7.7)	6.9 (5.5–8)	7.5 (6.5–8.2)
Adiponectin (pg/mL), median (IQR)	4.8 (3.4–6.7)	7.2 (3.6–8.8)	5.9 (3.6–8.9)	7.3 (4.3–11.2)

25OHD = 25-hydroxyvitamin D; BMI = body mass index; HDL, high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; HgbA1C = hemoglobin A1C; IL = interleukin; iPTH = intact parathyroid hormone; IQR = interquartile range; SE = standard error; TNF-α = tumor necrosis factor α.

25OHD levels. A significant percentage of our subjects had 25OHD concentrations below 20 ng/mL, but none had levels below 10 ng/mL. An effect from supplementation might have been seen in a more deficient cohort [23,24].

Sufficient body stores of 25OHD in adults have been defined as a serum 25OHD of at least 20 or 30 ng/mL [25,26]. In the pediatric population, there is not sufficient evidence to support a threshold greater than 20 ng/mL [27]. The threshold of 25OHD needed to influence inflammation has not been established. Daily supplementation with ergocalciferol at 2000 IU/day was inadequate to maintain serum 25OHD above 32 ng/mL in teens with inflammatory bowel disease. Despite this, subjects supplemented with 2000 IU daily had a lower incidence of elevated inflammatory markers than those receiving only 400 IU [28].

We observed few associations between serum 25OHD concentrations at baseline and BMI, inflammatory markers, and

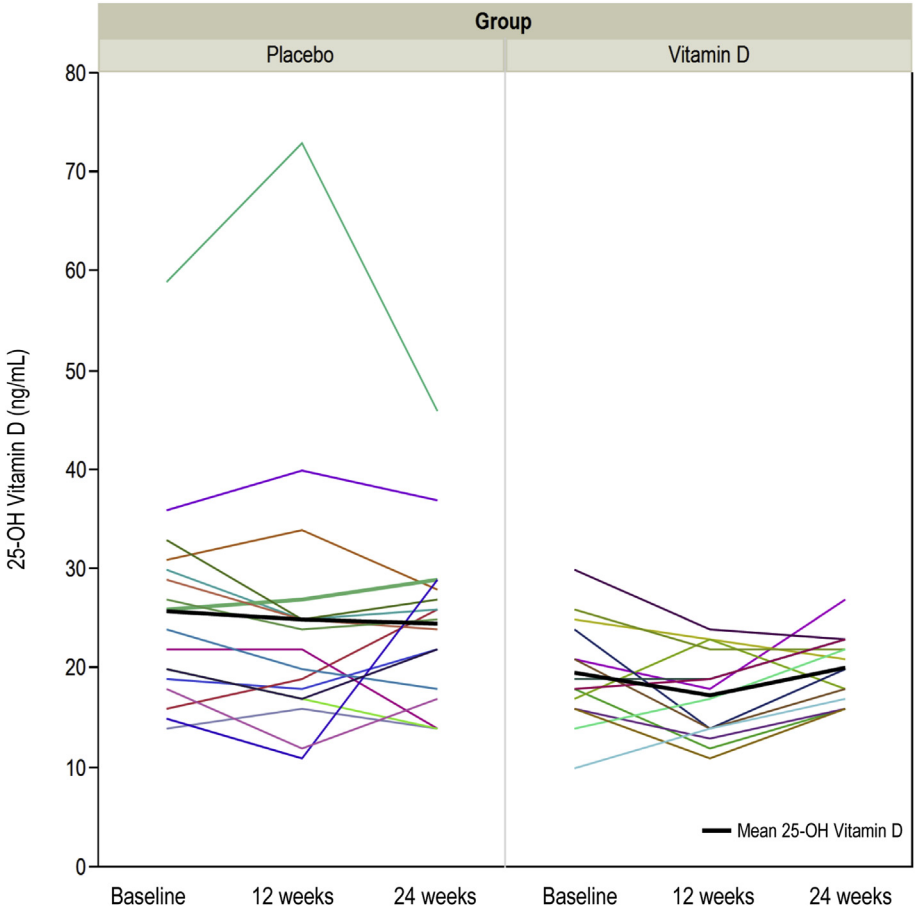

Figure 2. Serum 25OHD levels at baseline, 12 weeks, and 24 weeks for all subjects that completed the study. There was no significant change in the mean 25OHD level over time in placebo or vitamin D supplemented groups.

cardiometabolic risk factors. Baseline 25OHD was inversely associated with BMI but not with other measured biological markers. Numerous studies have shown a similar inverse relationship between serum 25OHD and BMI [8,29]. Prior pediatric studies have demonstrated direct correlations between 25OHD and adiponectin and high-density lipoprotein, whereas correlations between 25OHD and hs-CRP and IL-6 are variant between studies ranging from positive to equivocal [3,30]. Our different observations may be explained by our sample population limited to only overweight and obese teens. Differences in cytokines and other inflammatory markers are greater when comparing lean and obese patients [9].

We recognize several limitations of this pilot study including the relatively small cohort size, use of a single supplementation protocol with ergocalciferol, and the assessment of serum at only three time points. Our study protocol did not adjust for seasonality, sun exposure, or dietary intake of vitamin D although all patients were instructed not to take supplemental vitamin D in excess of 400 IU.

Despite these weaknesses, findings from this randomized controlled trial of vitamin D supplementation in overweight and obese teens offer important information. We add to available observational data on IL-6, TNF-α, and IL-10 concentrations in generally healthy overweight and obese adolescents. We focused on changes in inflammatory cytokines which had not been done in earlier studies of obese youth [12,13]. Our experience underscores the need for dose-response studies to establish the dose, formulation, and frequency of vitamin D supplementation needed to increase 25OHD in this population. Only when this is established will it be possible to determine if vitamin D supplementation can effectively reduce markers of inflammation and cardiovascular risk. These studies are worthy of pursuit given the alarming rates of obesity and its comorbidities in the adolescent population.

Acknowledgments

The authors acknowledge the Stanford Human Immune Monitoring Center (Holden T. Maecker, Ph.D., and Yael Rosenberg-Hasson, Ph.D.), Steven Chinn, Pharm.D., John S. Tamaresis, Ph.D., RedCap supported by National Institutes of Health (NIH)/National Center for Research Resources grant UL1 RR025744, and Mary Walter, Ph.D., Director, Clinical Research Core Laboratory, NIH. Results from this study were presented at the Pediatric Academic Society/Pediatric Endocrine Society Poster Symposium, 2013.

Funding Sources

This study was supported by the GlaxoSmithKline Junior Faculty Fund and Siegelman Fund, Department of Pediatrics, Stanford University.

References

[1] Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of high body mass index in US children and adolescents, 2007-2008. JAMA 2010;303:242–9.
[2] Dolinsky DH, Armstrong S, Mangarelli C, et al. The association between vitamin D and cardiometabolic risk factors in children: A systematic review. Clin Pediatr 2013;52:210–23.
[3] Parikh S, Guo DH, Pollock NK, et al. Circulating 25-hydroxyvitamin D concentrations are correlated with cardiometabolic risk among American black and white adolescents living in a year-round sunny climate. Diabetes Care 2012;35:1133–8.
[4] Ford ES, Zhao G, Tsai J, et al. Associations between concentrations of vitamin D and concentrations of insulin, glucose, and HbA1c among adolescents in the United States. Diabetes Care 2011;34:646–8.
[5] Alemzadeh R, Kichler J, Babar G, et al. Hypovitaminosis D in obese children and adolescents: Relationship with adiposity, insulin sensitivity, ethnicity, and season. Metabolism 2008;57:183–91.
[6] Menezes AR, Lamb MC, Lavie CJ, et al. Vitamin D and atherosclerosis. Curr Opin Cardiol 2014;29:571–7.
[7] Martins D, Wolf M, Pan D, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: Data from the Third National Health and Nutrition Examination Survey. Arch Intern Med 2007;167:1159–65.
[8] Turer CB, Lin H, Flores G. Prevalence of vitamin D deficiency among overweight and obese US children. Pediatrics 2013;131:e152–161.
[9] Mauras N, Delgiorno C, Kollman C, et al. Obesity without established comorbidities of the metabolic syndrome is associated with a proinflammatory and prothrombotic state, even before the onset of puberty in children. J Clin Endocrinol Metab 2010;95:1060–8.
[10] Roth CL, Kratz M, Ralston MM, et al. Changes in adipose-derived inflammatory cytokines and chemokines after successful lifestyle intervention in obese children. Metabolism 2011;60:445–52.
[11] Dong Y, Stallmann-Jorgensen IS, Pollock NK, 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.
[12] Nader NS, Aguirre Castaneda R, Wallace J, et al. Effect of vitamin D3 supplementation on serum 25(OH)D, lipids and markers of insulin resistance in obese adolescents: A prospective, randomized, placebo-controlled pilot trial. Horm Res Paediatr 2014;82:107–12.
[13] Belenchia AM, Tosh AK, Hillman LS, et al. Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: A randomized controlled trial. Am J Clin Nutr 2013;97:774–81.
[14] Ward KA, Das G, Roberts SA, et al. A randomized, controlled trial of vitamin D supplementation upon musculoskeletal health in postmenarchal females. J Clin Endocrinol Metab 2010;95:4643–51.
[15] Al-Shaar L, Mneimneh R, Nabulsi, et al. Vitamin D3 dose requirement to raise 25-hydroxyvitamin d to desirable levels in adolescents: Results from a randomized controlled trial. J bone mineral Res: Official J Am Soc Bone Mineral Res 2014;29:944–51.
[16] Maalouf J, Nabulsi M, Vieth R, 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.
[17] El-Hajj Fuleihan G, Nabulsi M, Tamim H, et al. Effect of vitamin D replacement on musculoskeletal parameters in school children: A randomized controlled trial. J Clin Endocrinol Metab 2006;91:405–12.
[18] Wortsman J, Matsuoka LY, Chen TC, et al. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72:690–3.
[19] Aguirre Castaneda R, Nader N, Weaver A, et al. Response to vitamin D3 supplementation in obese and non-obese Caucasian adolescents. Horm Res Paediatr 2012;78:226–31.
[20] Hollis BW, Wagner CL. Clinical review: The role of the parent compound vitamin D with respect to metabolism and function: Why clinical dose intervals can affect clinical outcomes. J Clin Endocrinol Metab 2013;98:4619–28.
[21] Gallagher JC, Jindal PS, Smith LM. Vitamin D supplementation in young White and African American women. J bone mineral Res: Official J Am Soc Bone Mineral Res 2014;29:173–81.
[22] Drincic A, Fuller E, Heaney RP, et al. 25-Hydroxyvitamin D response to graded vitamin D3 supplementation among obese adults. J Clin Endocrinol Metab 2013;98:4845–51.
[23] Didriksen A, Grimnes G, Hutchinson MS, et al. The serum 25-hydroxyvitamin D response to vitamin D supplementation is related to genetic factors, BMI, and baseline levels. Eur J Endocrinol 2013;169:559–67.
[24] Binkley N, Gemar D, Engelke J, et al. Evaluation of ergocalciferol or cholecalciferol dosing, 1,600 IU daily or 50,000 IU monthly in older adults. J Clin Endocrinol Metab 2011;96:981–8.
[25] Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. J Clin Endocrinol Metab 2011;96:53–8.
[26] Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911–30.
[27] Misra M, Pacaud D, Petryk A, et al. Vitamin D deficiency in children and its management: Review of current knowledge and recommendations. Pediatrics 2008;122:398–417.
[28] Pappa HM, Mitchell PD, Jiang H, et al. Maintenance of optimal vitamin D status in children and adolescents with inflammatory bowel disease: A randomized clinical trial comparing two regimens. J Clin Endocrinol Metab 2014;99:3408–17.
[29] Reis JP, von Muhlen D, Miller 3rd ER, et al. Vitamin D status and cardiometabolic risk factors in the United States adolescent population. Pediatrics 2009;124:e371–9.
[30] Williams DM, Fraser A, Sayers A, et al. Associations of 25-hydroxyvitamin D2 and D3 with cardiovascular risk factors in childhood: Cross-sectional findings from the Avon Longitudinal Study of Parents and Children. J Clin Endocrinol Metab 2012;97:1563–71.