European Journal of Pediatrics
https://doi.org/10.1007/s00431-020-03831-0

ORIGINAL ARTICLE

Response to single oral dose vitamin D in obese vs non-obese vitamin D–deficient children

Akshay Tayde[1] · Medha Mittal[1] · Rajesh Khadgawat[2] · Shikha Sharma[3] · V Sreenivas[4] · Anuradha Rai[1]

Received: 18 August 2020 / Revised: 28 September 2020 / Accepted: 5 October 2020

Abstract

Obese individuals are prone to vitamin D deficiency because of sequestration of vitamin D in their body fat. We planned to evaluate the rise in serum 25(OH)D levels in vitamin D–deficient obese vs normal body mass index(BMI) children, after administration of identical single dose of vitamin D. Twenty-two obese and 22 normal BMI children with serum 25 (OH)D < 20 ng/mL were given single oral dose 150,000 IU vitamin D, and 25 (OH)D levels were measured at 1 week and 1 month post-intervention. Results show that rise in 25(OH)D level from baseline was about 2.2 times lesser in obese compared with children with normal BMI, both at 1 week and at 1 month. The rise in 25(OH)D from baseline to 1 month was inversely correlated to BMI ($r = -0.56$, $p = < 0.001$), waist circumference ($r = -0.48$, $p = 0.001$), total fat mass ($r = -0.58$, $p < 0.001$), and fat mass index ($r = -0.59$, $p < 0.001$).

Conclusion: The obese children have a 2.2 times lower rise in serum vitamin D levels as compared with the normal BMI children for the same dose of vitamin D supplementation.

What is Known:
• *The obese individuals are prone to vitamin D deficiency and may be given higher doses of vitamin D supplementation.*

What is New:
• *Our study demonstrates that obese children have 2.2 times lesser rise in serum 25(OH)D concentrations as compared with normal BMI children when administered similar oral dose vitamin D.*

Keywords Vitamin D · 25(OH)D · Deficiency · Obese · BMI · Fat mass

Abbreviations

ALP	Alkaline phosphatase
BMI	Body mass index
nBMI	Normal BMI
Ca	Calcium
DXA	Dual-energy X-ray absorptiometry
FMI	Fat mass index
iPTH	Intact parathormone
P	Phosphate
25(OH)D	Serum 25(OH)D
SD	Standard deviation
SPSS	Statistical Package for Social Science

Communicated by Peter de Winter

✉ Medha Mittal
goelmedha@gmail.com

[1] Department of Pediatrics, Chacha Nehru Bal Chikitsalaya, Delhi 110031, India

[2] Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi, India

[3] Department of Biochemistry, Chacha Nehru Bal Chikitsalaya, Delhi, India

[4] Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India

Introduction

It is increasingly being recognized that obese individuals are prone to vitamin D deficiency [1–6]. Sequestration of vitamin D in the adipose tissue mass seems to be largely responsible for it [7]. Deficiency of vitamin D in the obese has been linked to impaired glucose tolerance and insulin resistance not only in adults but also in children [8].

The definitions of vitamin D deficiency and insufficiency suggested by different expert groups vary widely and so do

Published online: 12 October 2020

the recommended treatment regimes for the same. Further, there are no clear guidelines for treating vitamin D deficiency in the obese. Though the Endocrine Society suggests that the obese be given 2 to 3 times higher daily doses (6000–10,000 IU/day) than the non-obese, there are no recommendations for weekly or single large doses which are more acceptable, convenient and practically feasible [9]. Further, these recommendations are based on a few studies in adults and a direct extrapolation of their results to treat obese children may not be an ideal approach [7, 10]. Thus, there is need to establish scientific evidence in the pediatric age group to assess the requirement of vitamin D in vitamin D–deficient obese children vis-a-vis those who are non-obese. This study was planned to evaluate the response to a single oral dose of vitamin D (150,000 IU) in vitamin D–deficient obese children and compare the same to that in children with normal body mass index (BMI).

Methods

This, open labeled, non-randomized interventional study was carried out at a tertiary care hospital from February 2019 to November 2019. The study was planned to evaluate and compare the response to single dose of oral vitamin D (150,000 IU) in vitamin D–deficient (serum 25(OH)D < 20 ng/mL) obese children vs children with normal BMI. The primary hypothesis was that the obese children would have less increase in 25(OH)D level in response to a single oral dose of vitamin D compared with children with normal BMI.

Participant selection Obese children (BMI more than 27th adult equivalent as per Indian Academy of Pediatrics (IAP) BMI charts) of age group 5 to 12 years presenting to pediatric endocrinology clinic for excessive weight were screened for inclusion [11]. Age- and sex-matched apparently healthy children with normal BMI (BMI less than 23rd adult equivalent of IAP BMI charts), presenting to pediatric OPD for minor complaints (like cough, coryza for less than 5 days), were also screened for inclusion.

The Asian population is known to have more adiposity and increased cardiometabolic risk at similar BMI values as their western counterparts, and hence, lower BMI cutoffs have been advocated to define overweight and obesity [12–14]. While adult BMI cutoff points of 25 kg/m^2 and 30 kg/m^2 define overweight and obesity, significant cardiometabolic risk was present at BMI of 23 kg/m^2 and further increased in BMI > 27.5 kg/m^2 in the Asians and hence overweight and obesity definitions were modified for this ethnic background population [14]. International Obesity Task Force (IOTF) has proposed that BMI values at 18 years be linked to child percentile curves to define overweight and obesity in childhood [15]. Accordingly, the Indian Academy of Pediatrics (IAP) recommend 23rd and 27th adult equivalent percentile curves of country specific data to define overweight and obesity in Indian children [11]. Hence, the obese and normal BMI participants were duly selected as per the recommended criteria for Indian population.

Children who received vitamin D supplements (more than 600 IU daily, i.e., more than their recommended daily allowance [16]) in the last 6 months were excluded. Similarly, children with already diagnosed systemic, endocrine, or metabolic disorder or receiving drugs which could interfere with vitamin D metabolism (anticonvulsants, steroids, antitubercular) were also excluded. After screening, additional exclusion criterion used was any subject with 25(OH)D level ≥ 20 ng/mL. Hence, all study subjects had 25(OH)D level < 20 ng/mL.

Ethical clearance was obtained from the institutional ethics committee. Written informed consent was obtained from either parent, and assent was obtained from children more than 7 years for participation in the study. Thus, 22 obese and 22 normal BMI (nBMI) children with 25(OH)D levels less than 20 ng/mL were enrolled.

Data collection The enrolled children were clinically evaluated including a thorough history and clinical examination. Weight was taken on a portable electronic scale accurate to 100 g with subjects dressed in minimal clothing and without footwear. Standing height was measured with a portable stadiometer accurate to 0.1 cm, placed on level floor, with the subject standing barefoot and his/her head level with the Frankfurt horizontal plane. Each measurement was taken twice and the average taken as the final value. The scale and stadiometer were calibrated using standard weight and height, respectively. BMI was calculated by dividing the weight in kilograms by square of height in meters. Waist circumference measurements were performed in accordance with the Anthropometry Procedures Manual, National Health and Nutrition Examination Survey (NHANES) [17]. Waist circumference measurements were performed with the child standing using a non-stretchable tape applied horizontally just above the upper lateral border of the right ileum. Each measurement was made at the end of a normal expiration and was recorded to the nearest 0.1 cm. Pubertal stage was assessed based on Tanner charts [18, 19]. All the observations and measurements were made by the same investigator. Total body fat was measured with dual-energy X-ray absorptiometry (DXA), and fat mass index (FMI) (fat mass in kg/height in m^2) was calculated. Obese subjects were asked to continue standard care (such as life style modification) as per the treating physician.

After an overnight fast, 4 mL venous sample was drawn for hemogram, liver and renal function tests, and serum total calcium (Ca), phosphate (P), alkaline phosphatase (ALP), 25(OH)D, and intact parathyroid hormone (iPTH). The

samples were immediately transported to the laboratory and analysis performed on the same day. For iPTH and 25(OH)D, the samples were centrifuged and stored at − 20 °C and analyzed within the next 7 days.

Intervention Vitamin D3 was given as a single oral dose of 150,000 IU in the form of chewable tablets (Eris Pharmaceuticals, Ahmedabad, India). All participants were given the same formulation along with milk, under direct supervision of the investigator to ensure compliance. The subjects were asked not to take any further vitamin D supplements till the completion of their follow-up.

Follow-up The participants were asked to follow-up after 7 days and 1 month of receiving the intervention. A reminder card was given, and telephonic calls were made to ensure the follow-up visits. At each visit, serum levels of 25(OH)D, iPTH, Ca, P, ALP, and urine calcium creatinine ratio were measured.

Safety analysis Serum total calcium (corrected) and urine calcium creatinine ratio were measured at 7 days and 30 days post-vitamin D dose to detect hypercalcemia and hypercalciuria, respectively. Parents and children were explained the symptoms of hypercalcemia, such as abdominal pain, vomiting, constipation, polyuria, and polydipsia, and were asked to report immediately if the child developed any such symptoms. At each follow-up visit, any such symptoms occurring in the intervening period were again enquired for.

Analytical methods Kidney and liver function tests, serum Ca, P, and ALP were performed on Beckman Coulter AU680 Analyzer. Serum 25(OH)D and iPTH were measured by chemiluminescence immunoassay (ACCESS-2 Beckman Coulter Immunoassay Analyzer; imprecision < 10% for 25(OH)D > 15 ng/mL and SD < 1.5 ng/mL for 25(OH)D < 15 ng/mL and imprecision < 8% for iPTH concentration > 12 pg/mL). Total body fat was assessed using dual-energy X-ray absorptiometry (fan beam technology using pediatric software for age < 16 years, DXA, Hologic QDR 4500A, Hologic Inc., Bedford, MA) with coefficient of variation of less than 5%. All measurements were done by a single trained technician.

Hypocalcemia was defined as corrected serum calcium < 8.8 mg/dL and hypercalcemia as corrected serum calcium > 10.8 mg/dL. 25(OH)D levels less than 20 ng/mL were classified as deficient [9] while levels > 100 ng/mL were defined as hypervitaminosis D [16]. Serum iPTH > 65 pg/mL were considered to be elevated. Urine calcium:creatinine ratio more than 0.25 mg/mg in age group 5–10 years and more than 0.21 mg/mg in 10–12 years age group was considered as hypercalciuria [20].

Outcome variables The primary outcome of interest was the rise in 25(OH)D levels in both the groups at 1 month. The secondary outcome variable was the safety analysis of single oral dose of 150,000 IU vitamin D as assessed by hypercalcemia and hypercalciuria at 1 week and 1 month, post-intervention.

Sample size calculation was based on a study by Camozzi et al. where rise in 25(OH)D after single oral dose of 300,000 IU cholecalciferol in 20 normal weight, and 14 obese adult females was studied. The mean rise in levels was 21.45 (SD 9.36) ng/mL in the obese group and 31.08 (SD 11.31) ng/mL in the normal weight group [21]. Based on this change, the sample size was computed (using nQuery software with 80% power, and alpha error of 5%) to be 19 for each group. Taking an attrition of 20%, a sample size of 22 participants in each group was considered adequate.

Statistical analysis and data management Details of all participants were recorded in a pre-designed case record pro forma, following which the data was entered in an Excel spreadsheet. The analysis was done using Statistical Package for Social Science (SPSS) software version 20. Data were tested for normality by Kolmogorov-Smirnov test and Shapiro-Wilk test. Mean with standard deviation was calculated for normally distributed data, and median with interquartile range (IQR) was calculated for skewed data. Independent sample *t* test and Mann-Whitney *U* test were applied to test the significance of differences between two means and medians, respectively. Correlations of vitamin D levels with different variables like BMI, fat mass, and fat mass index (FMI) were made using Pearson's correlation coefficient. p value < 0.05 was considered significant.

Results

Total 56 children (24 in obese group; 32 in normal BMI group) were screened, of which 12 (2 in obese group; 10 in normal BMI group) had 25(OH)D ≥ 20 ng/mL and, hence, excluded. Thus, 22 subjects in each group were recruited. All 22 subjects in obese group and 20 in normal BMI group completed the study. The demographic profile and physical parameters of the study population are presented in Table 1. All the study subjects were pre-pubertal, and the two groups were similar with respect to mean age and male:female ratio.

At baseline, mean 25(OH)D levels were similar in both the groups (14.01 ± 3.49 ng/mL in obese and 15.27 ± 4.75 ng/mL in nBMI group, $p = 0.321$)(Fig. 1; Table 2). However, serum iPTH and serum ALP levels were higher in the obese group (Fig. 2; Table 2). Post-intervention, the mean 25(OH)D concentration levels increased to 80.5 ng/mL in nBMI and 42.8 ng/mL in obese group at 1 week. The values at 1 month were 51.1 ng/mL and 29.9 ng/mL, respectively (Table 2). The

Table 1 Baseline parameters of the study population

Baseline characteristics	Obese ($n = 22$)	nBMI ($n = 22$)	p value
Mean age (months)	107.7 ± 20.7	105.8 ± 20.5	0.76*
Male:female	12:10	10:12	0.546#
Weight in kg (mean ± SD)	45.8 ± 9.5	23.6 ± 7.0	< 0.001*
Height (cm) (mean ± SD)	133.6 ± 11.2	125 ± 14.6	0.033*
BMI (mean ± SD) (kg/m^2)	25.39 ± 2.53	14.8 ± 1.48	< 0.001*
Waist circumference (cm) (mean ± SD)	80.2 ± 6.3	53.2 ± 8.0	< 0.001*
Total fat mass (kg) (mean ± SD)	20.2 ± 4.9 ($n = 20$)	6.38 ± 1.8 ($n = 18$)	< 0.001*
Fat mass index (kg/m^2) (mean ± SD)	11.13 ± 1.65 ($n = 20$)	4.32 ± 1.18 ($n = 18$)	< 0.001*

*Two sample t test

Independent samples Mann-Whitney U test

rise in 25(OH)D level from baseline was 2.2 times lower in obese subjects than in the nBMI group at the 1-month visit.

At 1 month, in obese group, 86.4% (19/22) had 25(OH)D levels > 20 ng/mL. This percentage in the nBMI group was 95% (25(OH)D > 20 ng/mL). Vitamin D sufficiency (25(OH)D > 30 ng/mL) at 1 month was achieved in 95% subjects with nBMI while only 50% of obese subjects could reach sufficiency. The rise in 25(OH)D from baseline to 1 week was inversely correlated to BMI ($r = -0.56$, $p = < 0.001$), waist circumference ($r = -0.48$, $p = 0.001$), total fat mass($r = -0.58$, $p < 0.001$), and FMI ($r = -0.59$, $p < 0.001$). Similarly, the rise in 25(OH)D from baseline to 1 month also had a significant negative correlation with BMI, waist circumference, total fat mass, and FMI but not with baseline 25(OH)D levels (Fig. 3). Regression analysis showed that for every 1 unit increase in BMI, the rise was reduced by 1.6 ng/mL. Further, the change in 25(OH)D levels from 1 week to 1 month also had a significant negative correlation with weight, BMI, fat mass, and FMI. Among other biochemical parameters, the serum iPTH levels were not significantly different at 1 month between the two groups, but serum ALP levels remained significantly higher in obese compared with nBMI subjects.

No serious adverse event occurred during the trial. None of the study subjects developed symptomatic hypercalcemia while asymptomatic hypercalcemia was seen in one subject in nBMI group at 1 week and in none in the obese group. Hypercalciuria was seen in 6 subjects (3 in obese and 3 in nBMI group) at 1 week and in one subject each in both the groups at 1 month. Hypervitaminosis D (25(OH)D levels > 100 ng/mL) was seen in four subjects with nBMI at 7 days post-supplementation while none of the obese had hypervitaminosis D.

Discussion

We sought to examine if identical doses of vitamin D result in a similar rise in vitamin D levels in vitamin D–deficient obese and normal BMI children of 5 to 12 years of age and observed

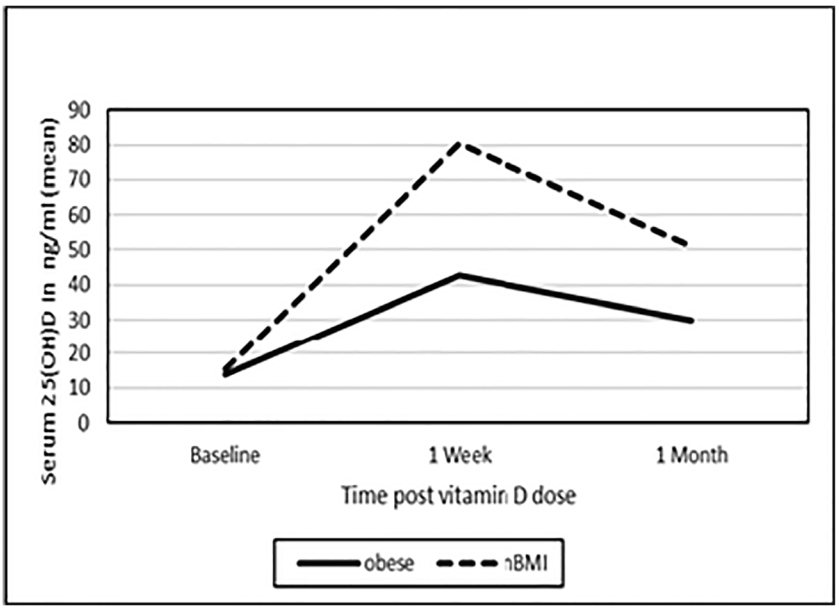

Fig. 1 Mean 25(OH)D at 1 week and 1 month of vitamin D dose in obese and normal BMI children

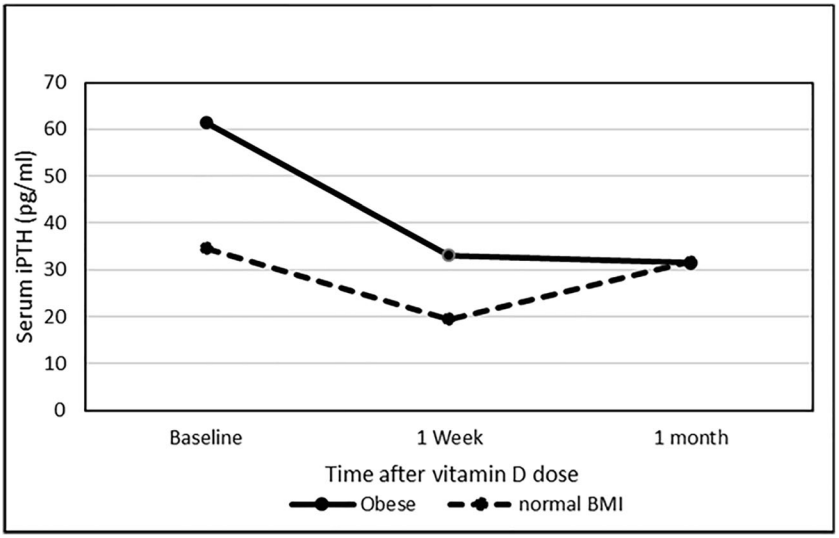

Fig. 2 Serum iPTH (median) at 1 week and 1 month of vitamin D dose in obese and normal BMI children

a clear difference between the two groups. Our results show that peak vitamin D response to a single dose of vitamin D is significantly less in obese subjects, compared with nBMI children. Not only was the rise in vitamin D level to 7 days but also the change from 1 week to 1 month post-supplementation was also inversely correlated to BMI and total fat mass. The rise in serum vitamin D level from baseline to 1 week and baseline to 1 month was 2.2 to 2.3 times lower in obese subjects than nBMI, and its fall from 1 week to 1 month was similarly affected. Among other parameters, ALP was significantly higher in the obese. This is in agreement with recent reports of high levels observed in the obese. The underlying mechanisms seem to be increased expression and activity of ALP in adipocytes and release of ALP from the adipose tissue into the circulation [22, 23]. ALP has also been shown to have a linear correlation with BMI and possibly contributes to leptin resistance in the obese [24].

The Endocrine Society suggests that the obese children and adults be given at least two to three times higher dose of vitamin D to treat vitamin D deficiency [9]. These recommendations are based on a single study by Wortsman et al. in which it was observed that the rise in blood levels of vitamin

Table 2 Biochemical parameters pre- and post-vitamin D dose

Parameters		Obese	nBMI	*p* value
Serum 25(OH)D (ng/mL) (mean ± SD)	Baseline	14.01 ± 3.49	15.27 ± 4.75	0.321*
	1 week	42.78 ± 14.7	80.50 ± 35.09	< 0.001*
	1 month	29.87 ± 9.41	51.14 ± 16.71	< 0.001*
Change in 25(OH)D (ng/mL) (mean ± SD)	Baseline to 1 week	28.77 ± 15.06	65.45 ± 34.56	< 0.001*
	Baseline to 1 month	15.86 ± 9.86	35.87 ± 16.99	< 0.001*
	1 week to 1 month	− 12.91 ± 10.98	− 28.68 ± 21.71	0.008*
Serum iPTH (pg/mL)	Baseline	61.45 (38.5)	34.6 (32.9)	0.012#
Median (IQ range)	1 week	32.95(23.3)	19.35 (29.3)	0.03#
	1 month	31.5 (15.9)	31.8 (28.2)	0.601#
Serum calcium (mg/dl) (mean ± SD)	Baseline	9.8 ± 0.25	9.9 ± 0.38	0.306*
	1 week	9.84 ± 0.24	10.21 ± 0.40	0.002*
	1 month	9.78 ± 0.37	9.87 ± 0.23	0.35*
Serum phosphate (mg/dl) (mean ± SD)	Baseline	4.96 ± 0.77	4.97 ± 0.55	0.96*
	1 week	5.4 ± 0.81	5.3 ± 0.42	0.65*
	1 month	5.15 ± 0.81	5.02 ± 0.64	0.57*
Serum ALP (mg/dl) (mean ± SD)	Baseline	371 ± 71.9	278 ± 56.7	< 0.001*
	1 week	335.1 ± 74.3	256.3 ± 66.6	0.001*
	1 month	315 ± 82.2	261.8 ± 54.6	0.017*

IQ interquartile

*Two sample t test

Independent samples Mann-Whitney *U* test

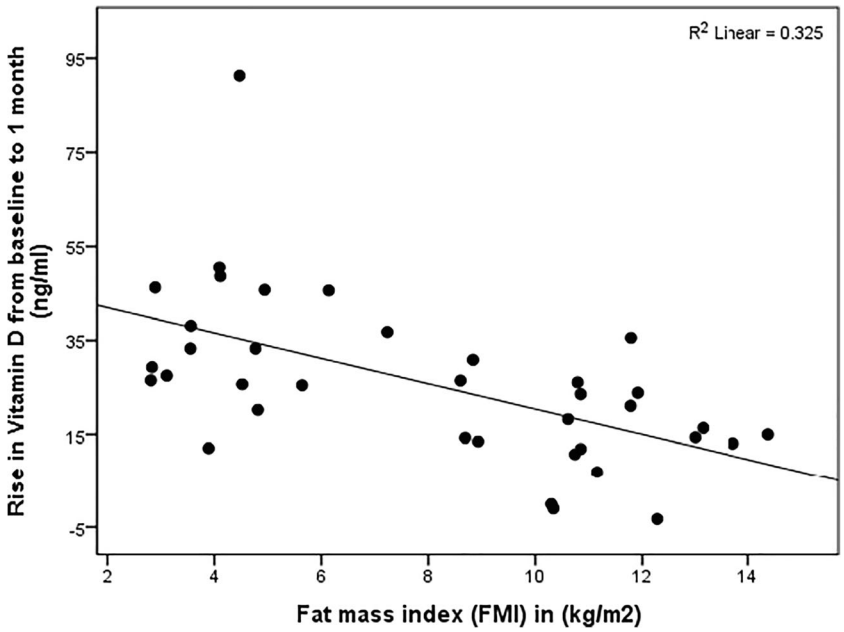

Fig. 3 Scatter plot depicting the strength of the correlation of rise in 25(OH)D from baseline to 1 month with fat mass index (FMI)

D was no more than 50% in obese compared with non-obese adults when either exposed to UV light or when given a single oral dose of 50,000 IU of vitamin D2 [7].

The response to single oral dose vitamin D supplementation in vitamin D–deficient obese subjects has not been studied in children. The only published study in pediatric age group was reported by Motlaghzadeh et al. [25]. They assessed response to oral vitamin D 50,000 IU weekly for 6 weeks (total 6 doses; levels measured 2 weeks after last dose) in obese ($n = 43$) and non-obese ($n = 30$) children with hypovitaminosis D (serum levels< 30 ng/mL). Approximately 56% (24/43) obese subjects had a level < 30 ng/mL while only 3.3% (1/30) subjects with nBMI had levels < 30 ng/mL. In that study, the baseline and post-treatment 25(OH)D levels had negative correlation with BMI.

Castaneda et al. evaluated post-supplementation rise in vitamin D levels in 18 obese and 18 age- and sex-matched non-obese adolescents using daily doses (2000 IU daily doses for 12 weeks) and observed a 1.7 times lower rise in vitamin D levels in the obese [26]. However, the supplementation was given irrespective of their vitamin D status being deficient or sufficient. However, change in vitamin D did not correlate with body weight. Since multiple doses of vitamin D supplementation were used, they could not assess effect on peak vitamin D levels.

The response to a single dose of vitamin D supplementation has been reported in adults. Camozzi et al., comparing response to 300,000 IU single-dose vitamin D in obese, overweight, and normal weight women, showed poorer response in the obese/overweight than normal weight subjects [21]. Similarly, Gallagher et al. too observed that the response to vitamin D supplementation was dependent on BMI [27].

The exact reason of poorer response in the obese in not known, but it is suggested that being fat soluble, vitamin D could be easily sequestrated in the adipose tissue. Obese, with higher body fat, may have higher sequestration resulting in lower levels. Recent studies suggest a markedly reduced expression of mRNA of 25-hydroxylase enzyme (CYP2R1) in the livers of obese mice compared with the livers of normal mice, and this may account for lower levels of 25(OH)D in the obese [28, 29]. Drincic et al. proposed that volumetric dilution in the large body volume rather than higher sequestration is responsible for lower levels [30]. But it does not explain slower fall after reaching peak at 1 week in obese subjects as observed in our study. Sequestration in fat, to some extent, may explain slower fall in obese as more vitamin D is released from adipose tissue. Besides, the change in levels from peak to 1 month would be a reflection of its pharmacokinetics. At a similar time after the dose (or at similar half-lives), the net change would be more in an individual in whom a higher level is reached. Hence, the change seems to be more in the nBMI group as the level reached was higher.

We did not find any correlation between changes in vitamin D levels with baseline vitamin D levels though the inclusion of participants with normal vitamin D status could have given more understanding on this aspect. Dhaliwal et al. and Castaneda et al. also did not find any correlation between the two [10, 26].

Although BMI is universally used for defining obesity, DXA is considered a better measure of total body fat (one of the gold standards) [31]. One of the most important drawbacks of BMI as a surrogate marker of fat is that it cannot differentiate between a muscular body and a fatty body. In our study, both BMI and total body fat (and also FMI) showed similar

correlations with rise in 25(OH)D level. All of our study subjects were pre-pubertal children; so adequate muscle mass development was yet to happen. A similar study in post-pubertal children may show a difference between BMI and total body fat.

Limitations of our study were many but most important was the absence of longer follow-up of 3 or 6 months which could have provided valuable information. The presence of subjects with extreme obesity might have highlighted more striking correlations.

Conclusions

Identical and single dose of oral vitamin D leads to 2.2 times lesser rise in 25(OH)D level at 1 month in obese children compared with nBMI children. The rise in 25(OH)D level was inversely correlated with body fat indices. To attain a similar increase in level of vitamin D as the nBMI children, obese children would require a higher dose of vitamin D or a repeat administration of the dose.

Authors' contributions AT: Data collection and analysis, drafting of the manuscript, approval of final manuscript. MM: conceptualization and design of study, data collection and analysis, drafting of manuscript and approval of final manuscript. RK: conceptualization and design of study, data analysis and interpretation, editing of manuscript and approval of final manuscript. SS: data collection and anlaysis, approval of final manuscript. SV: conceptualization and design of study, data analysis and interpretation, approval of final manuscript. AR: data collection, approval of final manuscript.

Compliance with ethical standards

The study was performed in line with ethical standards of Helsinki Declaration.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Ethical Approval was obtained from Institutional Ethics Committee, Chacha Nehru Bal Chikitsalaya, Delhi.

References

1. Garanty-Bogacka B, Syrenicz M, Goral J, Krupa B, Syrenicz J, Walczak M, Syrenicz A (2011) Serum 25-hydroxyvitamin D (25-OH-D) in obese adolescents. Endokrynol Pol 62(6):506–511
2. Harel Z, Flanagan P, Forcier M, Harel D (2011) Low vitamin D status among obese adolescents: prevalence and response to treatment. J Adolesc Health 48(5):448–452
3. Shin YH, Shin HJ, Lee YJ (2013) Vitamin D status and childhood health. Korean J Pediatr 56(10):417–423
4. Turer CB, Lin H, Flores G (2013) Prevalence of vitamin D deficiency among overweight and obese US children. Pediatrics. 131(1):e152–e161
5. Alemzadeh R, Kichler J, Babar G, Calhoun M (2008) Hypovitaminosis D in obese children and adolescents: relationship with adiposity, insulin sensitivity, ethnicity, and season. Metabolism. 57(2):183–191
6. Delvin EE, Lambert M, Levy E, O'Loughlin J, Mark S, Gray-Donald K, Paradis G (2010) Vitamin D status is modestly associated with glycemia and indicators of lipid metabolism in French-Canadian children and adolescents. J Nutr 140(5):987–991
7. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF (2000) Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 72:690–693
8. Peterson CA, Tosh AK, Belenchia AM (2014) Vitamin D insufficiency and insulin resistance in obese adolescents. Ther Adv Endocrinol Metab 5(6):166–189
9. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM, Endocrine Society (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96:1911–1930
10. Dhaliwal R, Mikhail M, Feuerman M, Aloia JF (2014) The vitamin D dose response in obesity. Endocr Pract 20:1258–1264
11. Indian Academy of Pediatrics Growth Charts Committee, Khadilkar V, Yadav S, Agrawal KK, Tamboli S, Banerjee M, Cherian A et al (2015) Revised IAP growth charts for height, weight and body mass index for 5- to 18-year-old Indian children. Indian Pediatr 52:47–55
12. Deurenberg-Yap M, Schmidt G, van Staveren WA, Deurenberg P (2000) The paradox of low body mass index and high body fat percent among Chinese, Malays and Indians in Singapore. Int J Obes 24:1011–1017
13. Yajnik CS (2002) The lifestyle effects of nutrition and body size on adult adiposity, diabetes and cardiovascular disease. Obes Rev 3: 217–224
14. WHO Expert Consultation (2004) Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 363(9403):157–163 Erratum in: Lancet. 2004 Mar 13;363(9412):902
15. Cole TJ, Lobstein T (2012) Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatr Obes 7(4):284–294
16. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, Michigami T, Tiosano D, Mughal MZ, Mäkitie O, Ramos-Abad L, Ward L, DiMeglio LA, Atapattu N, Cassinelli H, Braegger C, Pettifor JM, Seth A, Idris HW, Bhatia V, Fu J, Goldberg G, Sävendahl L, Khadgawat R, Pludowski P, Maddock J, Hyppönen E, Oduwole A, Frew E, Aguiar M, Tulchinsky T, Butler G, Högler W (2016) Global consensus recommendations on prevention and management of nutritional rickets. J Clin Endocrinol Metab 101: 394–415
17. Centers for Disease Control and Prevention (CDC) (2013) National Center for Health Statistics (NCHS). Anthropometry procedures manual. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. https://wwwn.cdc.gov/nchs/data/nhanes/2013-2014/manuals/2013_Anthropometry.pdf. Accessed Nov 16, 2019
18. Marshall WA, Tanner JM (1970) Variations in the pattern of pubertal changes in boys. Arch Dis Child 45:13–23
19. Marshall WA, Tanner JM (1969) Variations in pattern of pubertal changes in girls. Arch Dis Child 44:291–303
20. Metz MP (2006) Determining urinary calcium/creatinine cut-offs for the paediatric population using published data. Ann Clin Biochem 43:398–401
21. Camozzi V, Frigo AC, Zaninotto M, Sanguin F, Plebani M, Boscaro M, Schiavon L, Luisetto G (2016) 25-Hydroxycholecalciferol response to single oral cholecalciferol loading in the normal weight, overweight, and obese. Osteoporos Int 27:2593–2602

22. Ali AT, Paiker JE, Crowther NJ (2006) The relationship between anthropometry and serum concentrations of alkaline phosphatase isoenzymes, liver enzymes, albumin, and bilirubin. Am J Clin Pathol 126:437–442
23. Ali AT, Ferris WF, Penny CB, Van der Merwe M-T, Jacobson BF, Paiker JE et al (2013) Lipid accumulation and alkaline phosphatase activity in human preadipocytes isolated from different body fat depots. J Endocrinol Metabol Diabetes SA 18:58–64
24. Khan AR, Awan FR, Najam SS, Islam M, Siddique T, Zain M (2015) Elevated serum level of human alkaline phosphatase in obesity. J Pak Med Assoc 65(11):1182–1185
25. Motlaghzadeh Y, Sayarifard F, Allahverdi B, Rabbani A, Setoodeh A, Sayarifard A, Abbasi F, Haghi-Ashtiani MT, Rahimi-Froushani A (2016) Assessment of vitamin D status and response to vitamin D3 in obese and non-obese Iranian children. J Trop Pediatr 62:269–275
26. Castaneda AR, Nader N, Weaver A, Singh R, Kumar S (2012) Response to vitamin D3 supplementation in obese and non-obese Caucasian adolescents. Horm Res Paediatr 78:226–231
27. Gallagher JC, Yalamanchili V, Smith LM (2013) The effect of vitamin D supplementation on serum 25(OH)D in thin and obese women. J Steroid Biochem Mol Biol 136:195–200
28. Roizen JD, Long C, Casella A, O'Lear L, Caplan I, Lai M, Sasson I, Singh R, Makowski AJ, Simmons R, Levine MA (2019) Obesity decreases hepatic 25-hydroxylase activity causing low serum 25-hydroxyvitamin D. J Bone Miner Res 34(6):1068–1073
29. Bouillon R, Bikle D (2019) Vitamin D metabolism revised: fall of dogmas. J Bone Miner Res 34(11):1985–1992
30. Drincic AT, Armas LA, Van Diest EE, Heaney RP (2012) Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. Obesity (Silver Spring) 20:1444–1448
31. Mazess RB, Barden HS, Bisek JP, Hanson J (1990) Dual-energy x-ray absorptiometry for total-body and regional bone-mineral and soft-tissue composition. Am J Clin Nutr 51(6):1106–1112