RESEARCH PAPER

Efficacy of Daily Supplementation of Milk Fortified With Vitamin D2 for Three Months in Healthy School Children: *A Randomized Placebo Controlled Trial*

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Objective: To evaluate the efficacy of daily supplementation of 200 mL milk fortified with 240 IU of vitamin D2 (ergocalciferol).

Design: Double-blind randomized controlled trial.

Settings: School-based study in Delhi between October and December, 2019.

Participants: 235 healthy children aged 10-14 years.

Intervention: Daily supplementation of 200 mL milk fortified with 240 IU of ergocalciferol in intervention group (*n*=119) and 200 mL of plain milk in control group (*n* =116) for 3 months.

Outcome Measures: Change in serum 25 hydroxy vitamin D (25(OH)D), parathyroid hormone (PTH), bone formation and resorption markers, and urinary calcium creatinine ratio (U-Ca/CrR).

Results: The mean (SD) baseline serum 25(OH) D level in control and fortification groups was 11.9 (3.8) and 11.4 (3.6) ng/mL (*P*=0.23), respectively. The serum 25(OH)D levels did not increase post-intervention with the dose used for fortification, but were significantly higher in intervention group as compared to control group [10.8 (3.4) *vs* 6.7 (3.5) ng/mL; *P*<0.001]. A higher proportion of secondary hyperparathyroidism was observed post-intervention in control (39%) than in intervention group (13.3%); *P*<0.001. Serum carboxy-terminal telopeptide levels were similar in both groups but the serum procollagen type1 N-terminal propeptide levels were higher in the control than intervention group (*P*<0.007), following supplementation.

Conclusion: Supplementation of milk fortified with approximately 240 IU vitamin D2 for three months did not achieve sufficient serum 25(OH)D levels in Indian children with vitamin D deficiency during winter.

Keywords: *Bone health, Deficiency*, *Food fortification, Secondary hyperparathyroidism.*

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Optimum calcium and vitamin D intake during childhood and adolescence helps achieve peak bone mass which acts as a safeguard against osteoporotic fractures later [1]. Consequences on overall health require a population based approach for prevention of vitamin D deficiency like food fortification [2], as therapeutic supplementation throughout life is not practical. A recent meta-analysis of the effects of vitamin D fortification showed good efficacy of fortified dairy products to increase vitamin D levels [2]. At present, systematic voluntary or mandatory fortification of milk and milk products is being undertaken only in few countries like Finland, Norway, Sweden, Canada and USA [3].

In view of vitamin D deficiency being a serious public health problem, Food Safety and Standards Authority of India (FSSAI) issued instructions for voluntary fortification of milk and oil with vitamin A and D2 to provide approximately one-third (200-300 IU/L) of the recommended daily dietary allowance [4]. However, the adequacy and efficacy of these doses of vitamin D2 need to be assessed in children.

We, therefore, undertook a double-blind randomized controlled trial in healthy school children to evaluate the efficacy of daily supplementation of 200 mL fortified milk (approximately 240 IU of vitamin D2) on the serum vitamin D levels. The secondary objectives included effect of this intervention on serum levels of calcium, parathyroid hormone, alkaline phosphatase and bone markers.

METHODS

This randomized double-blind parallel placebo controlled study was conducted from October 1, 2019 (autumn) to December 30, 2019 (winter). The study protocol was approved by the Institutional Ethics Committee and the trial was registered prospectively at the clinical trial registry of India. Apparently healthy school children, aged 10-14 years, who consented were recruited from two fee- paying schools in Delhi following approval from the school management. Written consent from parents of eligible children and written assent from children was solicited. Children with clinical features of rickets, history of any chronic systemic illness, renal stones, history of milk allergy, intake of vitamin D in last six months in doses exceeding 600 IU/day or if consuming drugs like steroids, anti-tubercular/anti-epileptic drugs were excluded.

Block randomization with varying block size of 2 or 4 was used within each school to allocate the children into fortified and control arm, respectively using the computer-generated randomization list. Allocation concealment was done using opaque envelopes which were prepared by a person other than investigators. Participants were assigned to one of the two groups as per the code by the respective class teachers. The participants and care providers were blinded to the randomization. The teachers knew the codes as group A and B but did not know whether milk in the respective group was fortified or not.

Two sets of strawberry flavored ultra-heat treated toned milk in sterilized and homogenized 200 mL tetra packs were provided in the month of September, 2019 for the study by Mother Dairy Fruit and Vegetable Pvt. Ltd, a licensed and registered firm by FSSAI. First set was provided with 1200 IU of vitamin D2 per litre of milk (approximately 240 IU of vitamin D2 in each tetra pack) whereas other set was without fortification. The tetra packs were similar in appearance, odor and taste with labels known only to the manufacturers. The shelf life of tetra packs containing fortified and unfortified milk was 120 days at normal ambient temperatures, and were required to be kept in cool, dry and pest free ambience. Samples of milk were collected randomly at the time of production and after completion of the study for stability and estimated by LC-MS method (AOAC 2016.05).

Intervention group received fortified milk whereas control group received unfortified milk for 3 months. Daily supplementation for 6 days a week was carried out at schools under the supervision of teachers and investigating staff. Tetra packs were provided to the parents every month for Sundays and planned holidays. Parents were advised to collect the tetra packes from the school for unplanned holidays. A Whatsapp group was created by each teacher with parents and chief co-ordinator for day-to-day communication, monitoring and ensuring compliance during planned and unplanned holidays.

Brief history and clinical examination including anthropometry were performed. Heights were measured to nearest 0.1 centimeter with portable Holtain stadiometer (Holtain Inc.) with the child positioned in the Frankfurt plane. Weights were measured to nearest 0.1 kg with the digital weighing machine. The weighing scale and stadiometer were calibrated using the standard weight and height, respectively. Children were advised against any change in lifestyle during the study period. Two day (one working day and one holiday) 24-hour dietary recall method and food frequency questionnaire were used to gather data on dietary pattern and nutrient intake at baseline. The consumption of calcium and vitamin D rich foods, and amount and type of milk and oil consumed (fortified or not) were also recorded. The household measures used for data collection were standardized in the laboratory to obtain the actual weight of raw foods going into each preparation. Subsequently the data on food consumption in household measures were converted into raw ingredients. The nutrient intakes were then obtained by using the Diet Cal software [5]. No dietary counselling was provided during the study period.

Blood samples were collected in the fasting state between 8-9 AM at baseline and after three months (end-line). They were centrifuged and serum separated into aliquots at the study site and transported in dry ice to the laboratory. Serum calcium, phosphate, alkaline phosphatase (ALP), 25-hydroxy vitamin D [25(OH)D], parathyroid hormone (PTH) and spot urinary calcium creatinine ratio (U-Ca/CrR) were estimated the next day. Two aliquots were frozen -70^{0}C for estimation of bone markers. Serum 25(OH)D was estimated by chemiluminescence (DiaSorin Inc.) and PTH by electrochemiluminescence method (Roche Diagnostics). Intra and inter-assay coefficient of variation was 3.5% and 5% for serum 25(OH)D and 2.4% and 3.6% for PTH. Serum 25(OH)D level of <20 ng/mL was defined as insufficiency and <12 ng/mL as vitamin D deficiency (VDD) [6]. Secondary hyperparathyroidism was defined as PTH >65 pg/mL. Serum calcium, phosphate and ALP were estimated by auto-analyzer Cobas C-501 (Roche Diagnostics). Serum bone markers viz., C-terminal crosslinked telopeptide of type 1 collagen (CTx-1) and propeptide of N-terminal of type 1 collagen (PINP) were measured by Elecsys 2010 based on principle of electrochemimmunoassay. U-Ca/CrR was estimated using Cobas C-3 (Roche Diagnostics) with a level >0.21 suggestive of hypercalciuria [7].

The sample size was calculated assuming baseline mean (SD) of serum 25(OH)D of 11.7 (5.36) ng/mL in both groups. Expecting no change in control group and an increase of 3 ng/mL in serum 25(OH)D levels after 3 months of supplementation with combined SD of 3 ng/mL [8], the estimated sample size was 68 per group. The assumed alpha error and power were 5% and 90%, respectively. The total number of subjects required for the study with 20% drop out rate was 90 per group.

Statistical analysis: Continuous variables were summarized as mean (SD) (normally distributed) or median (Q1,Q3) (non-normally distributed). Categorical variables were presented as proportions. Baseline characteristics were compared between the groups using unpaired *t*-test or Chi-square test as appropriate. Intention-to-treat (ITT) analysis was done for effect on serum 25(OH)D and serum PTH levels and per protocol (PP) analysis was carried out for other biochemical variables. All the outcomes were compared between the groups using unpaired *t*-test/ Wilcoxon rank sum test and within the group (from baseline to 3-months) using paired *t*-test/Wilcoxon signed rank test. The results were presented as difference and 95% confidence interval. *P* value less than 0.05 was considered statistically significant.

RESULTS

The flow of the study participants is shown in **Fig. 1**. **Table I** shows the baseline demographic characteristics. No child from either of the group reported any discomfort or gastrointestinal side-effects after consuming milk. Samples of milk were collected randomly at the time of production and on completion of the study for stability, which showed serum 25(OH)D levels of 236 IU/200 mL and 221 IU/200 mL, respectively indicating <10% variation.

The baseline serum 25(OH)D levels were similar in the control and fortification groups (**Table I**), with significantly higher end-line levels in the intervention than in the control group as shown in **Table II**. The number of subjects with vitamin D deficiency and insufficiency at baseline were 70 (60%) and 46 (40%) in the control group and 65 (54.6%) and 54 (45.4%) in the intervention group, respectively (*P*=0.37). Vitamin D deficiency, insufficiency and sufficiency after three months were noted in 101 (97%), 3 (3%), 0 in control and 74 (70%), 31 (29%), 1 (1%) in the intervention group, respectively (*P*<0.001). The median (Q1,Q3) percentage rise in serum 25(OH) D was significantly higher among subjects with serum 25 (OH)D levels <12 ng/mL [*n*=58, 10.64 (–48.71, –5.66)] than those with levels >12 ng/mL [*n*=48, -20.41 (–34.36, –7.67)] in the intervention group (*P*<0.001). There was poor

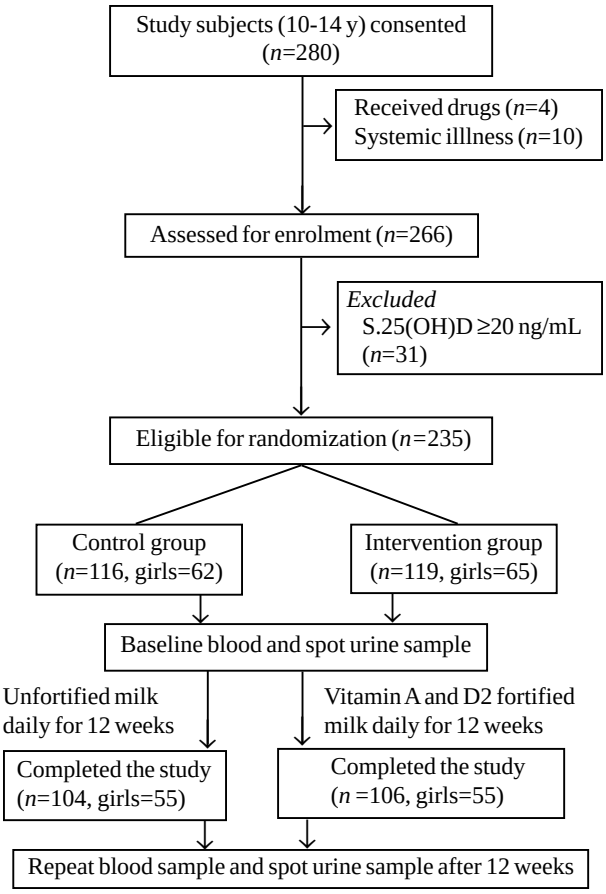

Fig. 1 CONSORT flow diagram for the study.

Table I Baseline Characteristics of the Study Population

Parameter	*Unfortified group (n=119)*	*Fortified group (n=116)*
Age, y	10.4 (0.8)	10.3 (0.5)
Body mass index, kg/m^2	16.8 (3.2)	16.7 (3.3)
Calcium, mg/dL	9.97 (0.3)	10.01 (0.3)
Phosphorus, mg/dL	5.02 (0.49)	5.01 (0.46)
ALP, IU/mL	258.83 (72.3)	253.49 (62.3)
25(OH)D, ng/mL	11.97 (3.79)	11.42 (3.63)
PTH, pg/mL[a]	45.8 (35.5, 60.0)	52.3 (35.3, 61.6)
CTX, pg/mL	1705.7 (483.2)	1685.4 (400.7)
PINP, ug/dL	655.3 (203.4)	679.9 (211.4)
Urine Ca: Cr ratio[a]	0.04 (0.01, 0.1)	0.05 (0.03, 0.09)

Data expressed as mean (SD) or [a]median (IQR); ALP-alkaline phosphatase, 25(OH)D- 25 hydroxy vitamin D, PTH- parathyroid hormone, CTX- C-terminal crosslinked telopeptide of type 1 collagen, PINP- propeptide of N-terminal of type 1 collagen, Ca:Cr- calcium: creatinine P>0.05 for all variables

Table II Biochemical Parameters After Intervention in Unfortified and Fortified Groups

Parameter	*Unfortified group (n=104)*	*Fortified group (n=106)*	*P value*
Calcium, mg/dL	9.88 (0.3)[c]	9.98 (0.3)	0.01
Phosphorus, mg/dL	4.97 (0.45)	4.96 (0.42)	0.80
ALP, IU/mL	273.24 (75.5)[c]	251.32 (57.7)	0.02
25 (OH)D,ng/mL[b]	6.73 (3.5)[a]	10.81 (3.5)	<0.001
PTH, pg/mL[b,a]	52.6 (38.8,75.2)[c]	46.5 (32.2,58.8)[c]	0.007
CTX, pg/mL	1023.22 (317.7)[c]	982.42 (304)[c]	0.35
PINP, ug/dL	736.33 (201.4)[c]	657.32 (216.5)	0.007
Urine Ca:Cr ratio[a]	0.04 (0.02,0.1)	0.04 (0.02,0.08)	0.86

All parameters are serum unless stated. [c]P<0.05 for intragroup comparison from baseline to post-intervention value. Data expressed as mean (SD) or [a]median (Q1, Q3). [b]n=116 and 119 in unfortified and fortified group, respectively (intention to treat analysis). ALP-alkaline phosphatase, 25(OH)D-25 hydroxy vitamin D, PTH-parathyroid hormone, CTX-C-terminal crosslinked telopeptide of type 1 collagen, PINP-propeptide of N-terminal of type 1 collagen, Ca:Cr-calcium: creatinine.

correlation between serum 25(OH)D and gender or BMI (P>0.05).

The prevalence of secondary hyperthyroidism increased from 18.1% to 39% (P<0.001) in the control group and decreased from 22.7% to 13.3% (P<0.001) in the intervention group, with significant inter-group difference (P<0.001). An inverse correlation was observed between serum 25(OH)D and PTH both at baseline in control (r=-0.23, P=0.01) and intervention groups (r=-0.29, P=0.001) and following supplementations in both groups (r= -0.23, P=0.01); (r= -0.29, P=0.001), respectively. No subject in either group developed hypercalciuria following supplementation.

The overall energy intakes were less (70.6%) than the RDA, with adequate protein intakes in the study group. The mean (SD) intake of calcium in intervention and control groups was 655.3 (224.1) and 617 (240.3) mg/day with dairy calcium contributing an intake of 57.4% and 58.4% in both groups. The vitamin D intake through fortified foods ranged from 17-97 IU/day in both the groups.

DISCUSSION

The present study demonstrated higher serum 25(OH)D levels following consumption of vitamin D2 fortified milk (240 IU/200 mL) for a period of 3 months as against consumption of unfortified milk, with significant decrease in secondary hyperparathyroidism.

Several studies in children have similarly observed higher serum 25(OH)D levels after consumption of vitamin D fortified milk than unfortified or no milk at all [2,3, 9]. Higher serum 25(OH)D levels were seen in children who consumed at least 450 mL/day of vitamin D fortified milk than those who drank < 300 mL/day after adjusting for age and sex [9].

The serum 25(OH)D levels did not increase above the baseline in the fortified group with the current levels of fortification; however, the decline was lesser than the unfortified group. This suggested that 240 IU of additional vitamin D2 through fortified milk for 3 months was not adequate during harsh winter months with high atmospheric pollution recorded in Delhi during the study period, when the availability of UVB rays was low [10,11]. Inadequate synthesis of vitamin D3 during winter months in children has been similarly reported earlier [12].

Vitamin D3 has higher efficacy than D2 in raising serum 25(OH)D levels [13-15]. However, whether fortification with D3 instead of D2 would have resulted in higher serum 25(OH)D levels is debatable and outside the purview of the current study. A rise in serum 25(OH)D levels was reported earlier with almost similar dose of 200 IU of D3 supplementation for 12 months [16], unlike no change observed in another study after 11 weeks of supplementation in healthy adolescents with baseline vitamin D sufficiency [17]. These contrasting observations could be because of varying baseline 25(OH)D levels, duration of intervention, vitamin D preparations and modes of supplementation. The rise in serum 25(OH)D was significantly higher in those with lower baseline serum 25(OH)D levels in the present study, as also reported earlier [8,16,18,19].

A significant reduction in serum PTH levels and secondary hyperparathyroidism in the intervention group suggests the role of even a small amount of vitamin D administered with calcium in reducing negative consequences on bone mineral metabolism. Similarly, inverse correlation between serum 25(OH)D and PTH levels have been documented earlier [16,18,20].

Earlier studies have not reported a significant effect on either bone formation or resorption markers [21,22]; however, a decrease in resorption markers like serum CTx and urinary deoxypyridiniline is reported following vitamin D supplementation [23,24]. In the present study, a significant decline in serum CTx levels in both the groups with no appreciable inter group differences, could be due to the additional calcium provided through milk. Similar observation was also reported in healthy premenopausal women following calcium supplementation [25]. No significant change in serum PINP levels following supplementation in the intervention

WHAT IS ALREADY KNOWN?

- Fortification of milk with vitamin D is an effective strategy for preventing vitamin D deficiency.

WHAT THIS STUDY ADDS?

- Consumption of 200 mL of fortified milk (containing 240 IU vitamin D2) for 12 weeks is inadequate in preventing vitamin D deficiency in school children from Delhi during winter season.

group concurs with earlier studies where bone specific ALP, serum osteocalcin and serum PINP remained the same [21,22,24]. These variations in bone markers following vitamin D supplementation may be due to differences in age of subjects, doses of vitamin D, duration of supplementation and baseline serum 25(OH)D etc. Spot U-Ca/CrR measured revealed no significant difference in the median U-Ca/Cr ratios at baseline and follow-up.

The main strength of the study was the evaluation of the efficacy of supplementing vitamin D2 fortified milk in children. The study; however, had limitations like absence of data on environmental pollution and sunlight exposure, lack of comparison with D3 fortified milk, and inability to carry out 24-hour urinary calcium excretion for definite diagnosis of hypercalciuria.

To conclude, supplementation of milk fortified with 240 IU Vitamin D2 for 12 weeks is not adequate to achieve vitamin D sufficiency, though it does reduce the decline in serum 25(OH)D levels during winter in prepubertal Indian children with vitamin D insufficiency.

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Ethics clearance: Institutional Ethics Committee, Maulana Azad Medical College; No. F.1/MAMC/IEC/(68/03/2019)/No 153, dated 09 August, 2019.
Contributors: RKM: conceptualizing and designing the study, clinical evaluation and preparation of the manuscript; AD,VD: clinical evaluation, analysis of data and preparation of manuscript; SY: designing the study and preparation of manuscript; SP: designing of dietary proforma, analysis of dietary data, manuscript preparation; AD: (Arjun Dang) Biochemical and hormonal evaluation, manuscript review; KV: sample size calculation and statistical analysis, manuscript preparation; PR: conceptualization and preparation of manuscript; SG: analysis of bone markers, manuscript review; AN: sample and data collection and data entry, manuscript review. All authors have read and approved the final manuscript.
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