Low Dose Depot Oral Vitamin D3 *Versus* Daily Oral Vitamin D3 for Treating Nutritional Rickets: A Randomized Clinical Trial

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ABBREVIATIONS

ALP ALKALINE PHOSPHATASE

CTRI CLINICAL TRIALS REGISTRY OF INDIA

HAZ HEIGHT FOR AGE Z-SCORE

MUACZ MID-UPPER ARM CIRCUMFERENCE Z-SCORE

PTH PARATHORMONE

TS THACHER SCORE

WAZ WEIGHT FOR AGE Z-SCORE

WHO WORLD HEALTH ORGANIZATION

WHZ WEIGHT FOR HEIGHT Z-SCORE

Abstract

Objective: To compare the efficacy of daily versus low dose depot oral vitamin D3 for treating nutritional rickets.

Design: Randomized Controlled Trial

Setting: Paediatrics department of a tertiary care hospital catering to semi-urban and rural population in Delhi, India

Methods: We randomized 66 children aged 3 months to 5 years with nutritional rickets to receive either daily oral vitamin D3 drops (3-12 months: 2000 IU; >12 months-5y: 4000 IU; n=33) for 12 weeks duration, or a single oral depot dose of vitamin D3 granules (3-12 months: 60,000 IU; >12 months-5y: 150,000 IU; n=33).

Results: Participants in both groups had comparable demographic characteristics, laboratory features and radiological severity of rickets. 33 participants in each group received the assigned intervention and all were followed up till 12 weeks. At 12 weeks follow up, children in both groups showed a significant improvement in all biochemical parameters [serum calcium, phosphorus, alkaline phosphatase, parathormone and 25(OH) vitamin D levels] as well as radiological healing. At 12 weeks, the mean (SD) serum 25(OH) vitamin D levels (nmol/L) were statistically comparable in both groups [daily: 120.2 (83.2), depot: 108 (74), P=0.43] and 31 (94%) children in each group had radiological healing (Thacher score <1.5). Two children in each group persisted to have raised alkaline phosphatase and one child each in the daily group continued to have hypocalcemia and hypophosphatemia at 12 weeks.

Conclusion: Low dose oral depot vitamin D3 is an effective alternative to daily oral vitamin D3 for nutritional rickets.

Keywords: Bone; Child; Health; Nutrition

INTRODUCTION

Vitamin D deficiency is a global health problem. Nutritional rickets is only the tip of iceberg representing widespread vitamin D deficiency with important public health implications[1]. There is a bouquet of treatment regimens for nutritional rickets incorporating vitamin D3 and/or calcium. Till not so long ago, rickets was treated with mega doses (300,000-600,000 IU) of vitamin D3[2-5]. Since then, the therapeutic efficacy and safety of lower doses of vitamin D3 (90,000-300,000 IU) for treatment of rickets has also been shown[6-10]. The Global Consensus Guidelines recommends that daily oral vitamin D3 at doses of 2000 IU to 4000 IU for at least 12 weeks duration may be used for treating nutritional rickets[11]. Daily dosage is considered to be more physiological and safer, although poor compliance and higher cost can be major concerns. However, studies directly comparing the therapeutic efficacy and safety of daily versus depot vitamin D3 for rickets in doses recommended by Global Consensus are scant. Stogmann, *et al.*[8] reported comparable efficacy of 400,000 IU vitamin D3 (given staggered as 200,000 IU on day 1 and day 3, orally) and daily 9600 IU of vitamin D3 drops for 18 days for rickets. Similarly, Akcam, *et al.*[9] found a comparable response in terms of radiological healing of rickets in children who received single dose of 600,000 IU of oral vitamin D3 or 20,000 IU/day of oral vitamin D3 for 30 days.

Hence, we conducted this trial to compare the efficacy of a low dose oral vitamin D3 given as depot versus daily oral vitamin D3 for 12 weeks' duration in under-five children with nutritional rickets in terms of improvement in serum 25-hydroxyvitamin D [25(OH)D] levels and radiological healing. We also intended to compare the two regimens in terms of improvement measured by proportion of children with hypocalcemia, hypophosphatemia, raised serum alkaline phosphatase (ALP) and raised parathormone (PTH) following treatment.

METHODS

This open label, randomized placebo-controlled study was conducted at a tertiary care hospital in Delhi, India, between November 2018 and April 2020. The study was approved by the Institutional Ethics Committee of the University College of Medical Sciences, New Delhi (IECHR/2018/36/116).

Sample size calculation

Sample size estimation was based on the study by Wadia, *et al.*[12] where in depot oral vitamin D3 therapy was compared with daily oral vitamin D3 in children with vitamin D insufficiency. The mean difference of serum 25(OH)D levels between baseline and after 16 weeks of therapy was 36 nmol/l in the daily group and 23 nmol/l in the depot group with standard deviation of change (post minus pre) in both groups of 17 nmol/l. To detect a difference of change in mean serum 25(OH)D levels of 13 nmol/l after 12 weeks of therapy between both groups at 80 % power and 5 % type I error with 1:1 ratio and two-sided, a sample of 28 patients in each group was needed. Considering attrition of 15 %, a sample size of 33 per group was estimated.

Enrolment

We assessed children aged 3 months to 5 years in the pediatric out-patient department for eligibility. Children with clinical (wrist widening, knock knees, bowed legs, frontal bossing, short stature, rachitic rosary etc.), biochemical (raised serum alkaline phosphatase with/without hypocalcemia and/or hypophosphatemia) and radiological evidence of rickets were eligible for inclusion. Radiological rickets was diagnosed based on Thacher score (TS) of radiographs of both knees and wrists[13]; scoring was done by a radiologist who was blinded for treatment allocation. TS $\geq$ 1.5 was considered as radiological rickets. Critically ill children, those having known malabsorption disorders, liver or renal insufficiency, or hypercalcemia were excluded. Children with a history of having received vitamin D, calcium supplements, or drugs affecting vitamin D metabolism (anticonvulsants, steroids, cancer chemotherapy) in previous 6 months were also excluded. Informed written consent was obtained from the child's caregiver.

Baseline assessment

We obtained a detailed history and performed a complete physical examination including anthropometric measurements. We estimated weight for age Z score (WAZ), height for Z score (HAZ), weight for height Z score (WHZ), and mid-upper arm circumference Z score (MUACZ) using AnthroCal software[14] and WHO reference charts[15]. We assessed serum calcium, phosphate, albumin, alkaline phosphatase, 25(OH)D and PTH levels at baseline. Radiographs of both wrists and knees were performed at baseline for all participants to assess severity of rickets.

Randomization and allocation concealment

We randomized 66 consecutive children with nutritional rickets to two groups (daily or depot vitamin D3 regimes) using a computer-generated block randomization sequence using 11 blocks of size 6 each at *www.randomization.com*. The randomization code was generated and concealed by a person not associated with the study. Allocation to either group was done using a sealed envelope technique.

Intervention, monitoring and follow up

Children in the "daily" group (n=33) received oral vitamin D3 given as drops [3-12 months: 2000 IU (2.5 ml once daily), 12months to 5 years: 4000 IU (5 ml once daily); Vitanova® drops, 800 IU/ml; Zuventus Healthcare Limited] for 12 weeks. Children in "depot" group (n=33) received a single oral dose of vitamin D3 granules [3-12 months: 60,000 IU (1 sachet), 12 months to 5 years: 150,000 IU (2.5 sachets); Vitanova® granules, one sachet = 60,000 IU, Zuventus Healthcare Limited] dissolved completely in 50 ml of milk under supervision. To enable accurate dispensing of vitamin D dose, we used a high precision (nearest 0.01 g) table top digital weighing scale (Mettler Toledo ®) to divide one sachet into two, where ever necessary. For exclusively breastfed babies, we counselled the mothers to express their breast milk and vitamin D3 granules were added to about 50 ml of expressed breast milk and then fed by cup/spoon. All children received daily oral calcium for 12 weeks [3-12 months: 250 mg;12 months to 5 years: 500 mg; Syrup Coralium®; 5 ml = 200 mg of elemental calcium, Zuventus Healthcare Limited]. If any child vomited the oral drug within 15 minutes of administration, it was noted and the drug was administered again per orally. Caregivers

in the "daily" group were provided with extra doses as buffer to cover for any wastage due to spillage or vomiting of the drug and they were asked to note the number of times they had to readminister the dose. One research team member (RS) was entrusted with the responsibility of ensuring compliance by contacting caregivers telephonically atleast once a week; report of any adverse events was also made. Compliance was checked by asking the parents to return the empty bottles of medicine to RS during their scheduled hospital visit. At the 4 weeks of follow up visit, we assessed serum calcium, phosphate, albumin and alkaline phosphatase. We measured serum calcium, phosphate, albumin, alkaline phosphatase, 25(OH)D, PTH levels and performed radiographic assessment of both wrists and knees, at the 12 weeks follow up.

Definition and measurement of outcomes

The primary outcome was the change in serum 25(OH)D following therapy at 12 weeks. The secondary outcomes were proportion of children with radiological healing (TS < 1.5), vitamin D deficiency, hypocalcemia (serum calcium < 8.5 mg/dl)[16], hypophosphatemia (serum phosphorous < 3.8 mg/dl)[17], hypercalcemia (serum calcium >10.8 mg/dl)[18], raised serum ALP (> 420 IU/l in infants, > 320 IU/l in 12 months to 5 years)[17], and hyperparathyroidism (serum PTH > 65 ng/l)[18] at 12 weeks. Vitamin D status ascertained by serum 25(OH)D levels was defined as: deficiency < 30 nmol/l, severe deficiency < 12.5 nmol/l, insufficient 30-50 nmol/l, sufficient 50 – 250 nmol/l and toxicity > 250 nmol/l[11].

Laboratory assessment

A venous blood sample (3 ml) was collected in vacutainers, spun and the serum stored at -20°C. Serum 25(OH)D and PTH levels were estimated after thawing the stored sera using radioimmunoassay-based kits (Beckman Coulter India Pvt. Ltd). Serum calcium, phosphorous, ALP and albumin were estimated using Beckmann Coulter Unicel Dxc 600 automatic analyzer. Serum calcium was corrected for serum albumin [corrected calcium (mg/dl) = measured calcium (mg/dL) + 0.8 X (4.0 – serum albumin (g/dl)[19].

Statistical analysis

The analysis was done using Statistical Package for the Social Sciences (SPSS) software version 26[20]. Shapiro-Wilk test was used to test for normal distribution of data. Mean (SD) of age, change in serum 25(OH) vitamin D, serum 25(OH) vitamin D, calcium, phosphorus, ALP, and PTH levels were compared between both groups using unpaired t-test. Median (interquartile range; IQR) was compared between the two groups using Mann–Whitney U-test. Proportions of children with radiological healing, vitamin D deficiency, hypocalcemia, hypophosphatemia, raised ALP, and hyperparathyroidism between the two groups were compared using Chi-square test or Fisher's exact test. Change in serum 25(OH)D levels within a group were assessed using paired t test. P values < 0.05 was considered as significant. A sensitivity analysis was performed to compare the response to daily versus depot vitamin D supplements in the subgroup of vitamin D deficient children.

RESULTS

Figure 1 depicts the enrolment of participants in the trial.

Baseline characteristics

Between December 2018 and November 2019, we enrolled 66 children (46 boys, 20 girls) with mean (SD, range) age 20.9 (10.6, 9 to 60) months; 33 each allocated to either treatment arm. 21 % of the participants were aged ≤12 months. Overall, 77.2 % of participants had delay in gross motor milestones, 27.2 % had irritability, 15.1 % had bony pains and 12.1 % had convulsions at the time of presentation to the hospital. The clinical signs on examination included wrist widening (90.9 %), frontal bossing (65.1 %), protuberant abdomen (42.4 %), rachitic rosary (36.3 %), bowing of legs (36.3 %), delayed closure of fontanelles (16.6 %) and knock knees (3 %). The baseline characteristics of 66 children enrolled is shown in Table 1. 60 % of children were vitamin D deficient at presentation; 40 % of these had severe vitamin D deficiency. Children receiving daily and depot vitamin D3 had comparable mean (SD) levels of baseline serum calcium, phosphorus, ALP, 25(OH)D and PTH as shown in Table 1. The median (IQR) TS of children in both groups at enrolment was statistically comparable [daily 8 (4.5-10); depot 8 (4.2-10), $P = 0.62$)].

Follow up

Both groups showed a good biochemical response to treatment at 4 weeks with a significant (P <0.001) rise in mean (standard deviation, SD) levels of serum calcium [daily 9.3 (0.6) mg/dl; depot 9.3 (0.5) mg/dl, P = 0.93], phosphorus [daily 3.9 (0.8) mg/dl; depot 4.4 (0.9) mg/dl, P = 0.02] and a significant (P < 0.001) fall in serum ALP levels [daily 399 (182) IU/l; depot 323 (142) IU/l, P = 0.03] compared to baseline estimates.

At 12 weeks, the serum calcium, phosphorous, ALP and PTH had normalized in almost all children and the proportions of children with hypocalcemia, hypophosphatemia, raised ALP, raised PTH or vitamin D deficiency were comparable in both the groups as shown in Table 2. At 12 weeks, the mean (SD) serum 25(OH)D levels increased significantly in both groups (P < 0.001); the rise was comparable in both groups [daily 90.5 (86.5) nmol/l; depot 82.7 (77) nmol/l; P = 0.70]. No child had severe vitamin D deficiency although two children continued to have vitamin D deficiency and another three had vitamin D insufficiency. At 12 weeks, the median (IQR) TS decreased significantly in both groups (P < 0.001); the median (IQR) TS were comparable in both groups [daily 0 (0-0); depot 0 (0-0); P = 0.44]. Radiographs at 12 weeks revealed healing (TS < 1.5) in 93.9 % children (31 per group) and 90.9 % children had TS of 0 (31 in daily group and 29 in depot group). Two children in the depot group had TS of 1 each, three children (two in depot group and one in daily group) had TS of 2 each and one child in daily group had TS score of 4.5, although none of them had evidence of vitamin D deficiency, hypocalcemia or hypophosphatemia. Overall, 26 children in the daily group and 28 children in the depot group had neither biochemical nor radiological evidence of rickets (P = 0.52).

A sensitivity analysis done in vitamin D deficient subgroup did not reveal any significant difference in therapeutic effects of either regimen as depicted in Table 3.

Compliance and adverse effects

All children were compliant with therapy and there was no loss to follow up. Hypervitaminosis D [serum 25(OH)D > 250 nmol/l] was seen in 3 children in the daily group and 1 child in the depot group, although they remained asymptomatic.

DISCUSSION

We found that oral low dose depot of vitamin D3 (60,000 IU in children aged 3-12 months and 150,000 IU in children aged 1-5 years) is an effective and safe alternative to daily oral vitamin D3 given for 12 weeks' duration for treating nutritional rickets in under-5 children without any increased risk of hypercalcemia. Both the regimens achieved comparable clinical, biochemical and radiological resolution without any adverse effects of therapy.

At 4 weeks follow up, we found that both groups showed significant rise in serum calcium and phosphorus and fall in serum alkaline phosphatase; the serum phosphorus levels being significantly higher in the depot group compared to daily group. At 12 weeks, however, the serum phosphorus was comparable in both treatment groups and hence this early rise in serum phosphorus in the depot group may be of little clinical benefit.

The increase in mean serum 25(OH)D levels was comparable in both groups despite the fact that the cumulative vitamin D3 dose in the daily group is twice that in the depot group. A subgroup analysis of the effect of the two treatment strategies in vitamin D deficient children with rickets, showed that both regimes were equally effective in terms of biochemical and radiological resolution of rickets as well as increase in serum 25(OH)D levels. In contrast, another study[12] has shown that in vitamin D deficient children, daily oral vitamin D3 supplements have fared better than low dose oral depot (100,000 - 200,000 IU) vitamin D3 doses in achieving and maintaining normalcy in serum vitamin D levels, although they increase the risk for hypervitaminosis D and hypercalcemia.

We found that three children in the daily group developed hypervitaminosis D and one child in the depot group developed hypervitaminosis D, although these children were asymptomatic and without concomitant hypercalcemia. Similar observations have been reported previously with the use of low dose oral vitamin D bolus in rickets[8,10]. None of the children in either groups had serum 25(OH)D levels exceeding 350 mmol/l reiterating the safety of both regimes. No child developed hypercalcemia in either groups. Previously, hypercalcemia was shown to be more likely with the use of higher oral depot doses of vitamin D (600,000 IU and 300,000 IU) compared to low dose

(150,000 IU) oral vitamin D bolus[6].

We found that four children (two per group) had TS ≥ 1.5 at the end of 12 weeks which might suggest the need for continued supplementation of vitamin D3 and calcium beyond 12 weeks in rickets. Contrasting to our figures of 91 %, Chatterjee, *et al.*[21] showed that only 47 % of children with rickets who received 600,000 IU of parenteral vitamin D3 had TS of 0 after 12 weeks in rickets. This emphasizes that radiological healing may take more than 12 weeks and continued therapy may be needed in a few cases of rickets.

The strengths of our study include a head-to-head comparison of a single low dose depot oral vitamin D3 with daily vitamin D3 therapy. A comprehensive assessment of clinical, biochemical and radiological parameters in a homogenous cohort empowers our study. A robust follow up and good compliance by all participants was possible in our study as one of the research team members was dedicated to carrying out follow up. Limitations of our study include the fact that we did not estimate hypercalciuria, another marker of safety profile of vitamin D supplementation. Only 21 % of our participants were aged ≤ 12 months and hence focused studies on infants evaluating efficacy of these regimens would be preferred. A prolonged follow up at 6-12 months post-treatment would be preferred to assess complete radiological resolution in the children with less than complete healing at 12 weeks and whether serum 25(OH)D sufficiency is sustained in the children post treatment.

CONCLUSIONS

A low dose oral depot vitamin D3 is an effective regimen to treat nutritional rickets in under-5 children. Compared to the daily oral vitamin D3 regimen, it offers the advantage of convenience and ease of administration.

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CLINICAL TRIAL REGISTRATION

Clinical Trials Registry of India (CTRI/2018/12/016760).

Conflict of interest: Zuventus Healthcare Ltd. India provided the drugs used in the study and are manufacturers of vitamin D and calcium formulations. They, however, had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

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RS: Study design, acquisition of data and analysis, drafting the manuscript, approved the final version.

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Legends for Figure

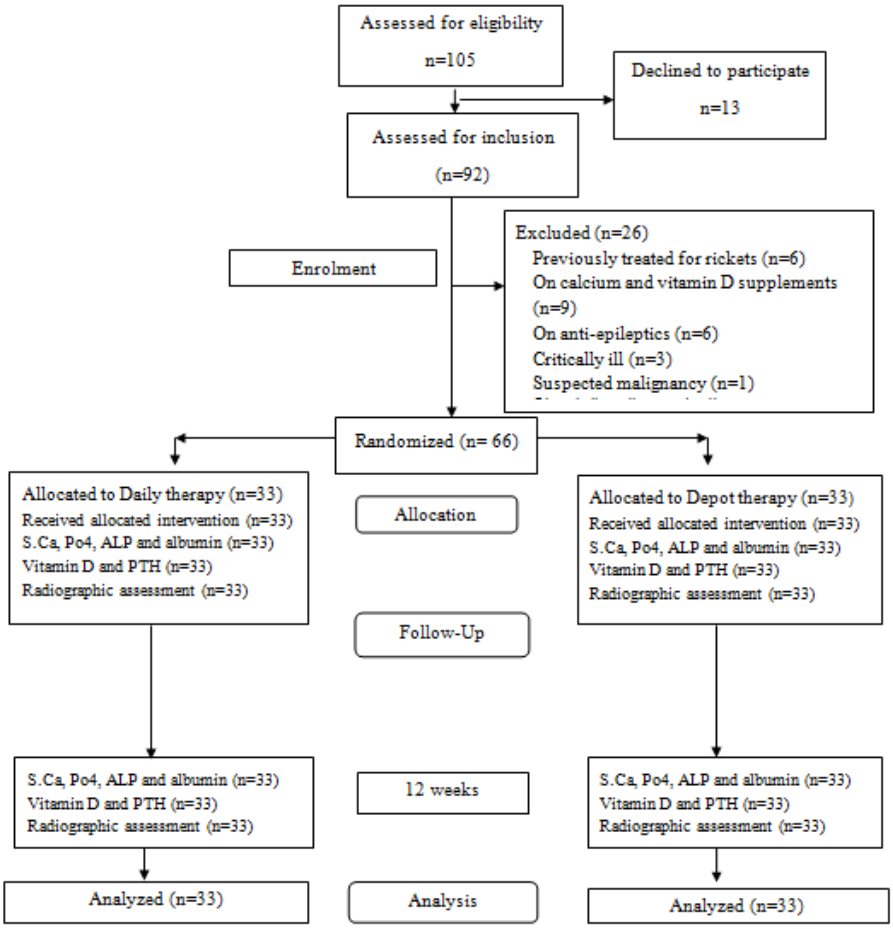

Figure 1. Flow of participants in the study entitled "Low Dose Depot Oral Vitamin D3 *Versus* Daily Oral Vitamin D3 for Treating Nutritional Rickets: A Randomized Clinical Trial"

Table 1. Baseline characteristics of children receiving low dose depot oral vitamin D3 *Versus* daily oral vitamin D3 for treating nutritional rickets

Baseline parameters	**Daily (n=33)**		**Depot (n=33)**	
	Mean	**SD**	**Mean**	**SD**
Age (months)	19.9	8.5	21.9	12.4
Weight for Age Z-score	-1.4	0.9	-1.4	0.9
Height for Age Z-score	-1.2	1.3	-1.3	1.2
Weight for Height Z-score	-1.20	0.90	-1.2	1.1
Mid Upper Arm Circumference Z-score	-1.1	0.7	-1.2	0.9
Serum calcium (mg/dl)	8.0	1.6	8.3	1.2
Serum phosphorus (mg/dl)	3.4	1.7	3.3	1.0
Serum alkaline phosphatase (IU/l)	870.1	393.8	802.4	329.8
Serum 25(OH)D (nmol/l)	29.7	20.2	25.7	20.2
Serum parathormone (ng/l)	299.3	287.1	289.2	267.1
Thacher score (TS)	7.1	2.9	7.2	2.9
	Number	**%**	**Number**	**%**
Male Sex	20	60.6	26	78.8
Exclusive breast feeding	32	96.9	31	93.9
Vitamin D status*				
Severe deficiency	7	21.2	9	27.3
Deficiency	19	57.6	21	63.6
Insufficiency	10	30.3	6	18.2
Sufficient	4	12.1	6	18.2
Hypocalcemia	19	57.6	15	45.5
Hypophosphatemia	25	75.8	24	72.7

P value > 0.05 for tests of differences between the 33 children each in daily and depot vitamin D3 group for all parameters. IQR interquartile range, SD standard deviation.

Table 2. Laboratory characteristics of children in daily and depot oral vitamin D3 at 12 weeks

Parameters	**Daily group (n=33)**		**Depot group (n=33)**		***P****
	Mean	**SD**	**Mean**	**SD**	
Serum calcium (mg/dl)	9.6	0.5	9.7	0.5	0.61
Serum phosphorous (mg/dl)	5	0.8	5	0.7	0.70
Serum ALP (IU/l)	253	71	241	59	0.59
Serum 25(OH)D (nmol/l)	120.2	83.2	108.0	74.0	0.43
Serum parathormone (ng/l)	36.6	34.5	29.1	24.9	0.64
Thacher score	0.2	0.8	0.2	0.5	0.93
	Number	**%**	**Number**	**%**	***P****
Vitamin D status					
25(OH)D <30 nmol/l	1	3.0	1	3.0	1.00
25(OH)D 30-50 nmol/l	1	3.0	2	6.1	0.64
25(OH)D >250 nmol/l	3	9.1	1	3.0	0.30
Hypocalcemia	1	3.0	0	0	1.00
Hypophosphatemia	1	3.0	0	0	1.00
Raised ALP	2	6.1	2	6.1	1.00
Hyperparathyroidism	3	9.1	1	3.0	0.30
Hypercalcemia	0	0	0	0	1.00
Radiological healing (TS<1.5)	31	93.9	31	93.9	1.00

ALP alkaline phosphatase, SD standard deviation, TS Thacher score

* *P* values for tests of differences between the 33 children each in daily and depot vitamin D3 group

Table 3. Laboratory characteristics of children with vitamin D deficiency in daily and depot groups at 0, 4 weeks and 12 weeks

Parameters	**Daily group (n=19)**		**Depot group (n=21)**		***P****
	Mean	**SD**	**Mean**	**SD**	
Serum calcium (mg/dl)					
• Baseline	7.9	1.6	8.2	1.2	0.68
• 4 weeks	9.2	0.7	9.2	0.6	0.76
• 12 weeks	9.6	0.6	9.7	0.5	0.89
Serum phosphorous (mg/dl)					
• Baseline	3.3	1.4	3.4	1.1	0.80
• 4 weeks	4	0.9	4.6	0.9	0.05
• 12 weeks	5.1	0.8	5.2	0.8	0.93
Serum ALP (IU/l)					
• Baseline	858	453	777	323	0.51
• 4 weeks	400	157	342	166	0.26
• 12 weeks	250	74	241	49	0.63
Serum 25(OH)D (nmol/l)					
• Baseline	16.0	8.0	12.7	6.7	0.18
• 12 weeks	137.5	103.7	110.5	86.2	0.38
Serum parathormone (ng/l)					
• Baseline	344.8	287.9	267.3	232.7	0.35
• 12 weeks	39.1	43.0	26.9	14.5	0.23
Thacher score (TS)					
• Baseline	6.8	3.2	6.9	3.2	0.88
• 12 weeks	0.2	1	0.1	0.5	0.71

ALP alkaline phosphatase, SD standard deviation

**P* values for tests of differences between the 19 vitamin D deficient children in the daily and 21 vitamin D deficient children in the depot vitamin D3 groups.