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**Original Research Article**

# Effect of vitamin D supplementation on growth parameters of children with vitamin D deficiency: a community based randomized controlled trial

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## ABSTRACT

**Background:** Vitamin D deficiency remains the most common cause of rickets globally and is highly prevalent in developing countries including India. This study aimed to compare the efficacy of vitamin D and calcium together with calcium alone on growth parameters of children with vitamin D deficiency in community based setting.
**Methods:** A randomized controlled trial was conducted in community based setting in Kanpur district. Multistage random sampling technique was used to select a total of 395 children between 2 years to 5 years from 5 villages of block Vidhunu. Of these, 138 children were randomized into two groups using balanced block randomization technique. Group 1 received vitamin D with calcium together and group 2 received calcium alone for a period of 12 months. Anthropometry, serum vitamin D, calcium, alkaline phosphatase levels were estimated at baseline and after 12 months. Data was analyzed using SPSS 20. Student's t test was used to analyze the differences in growth and laboratory parameters in the two groups. Multiple linear regression analysis was used to assess the effect of various factors on the growth parameters.
**Results:** Prevalence of vitamin D deficiency was 78.7%. Baseline characteristics of both groups were similar. After 12 months, group 1 demonstrated significantly greater improvement in weight SD score (21.4%) and height SD score (10.3%) and growth velocity (9.1 cm/year) compared to group 2 (14.3%, 7.8% and 6.9 cm/ year respectively). Also subjects in group 1 showed significantly greater improvement in serum levels of vitamin D, calcium and alkaline phosphatase than group 2.
**Conclusions:** Vitamin D supplementation along with calcium improves the growth of children. Regular supplementation of all children with vitamin D can be considered as a policy for prevention of malnutrition.

**Keywords:** Calcium, Children, Malnutrition, Supplementation, Vitamin D

## INTRODUCTION

Vitamin D deficiency is now considered to be the most common nutritional deficiency and one of the most common medical conditions which is undiagnosed.[1] Vitamin D can be synthesized in skin epithelial cells, but is not abundantly available in foodstuffs. Vitamin D deficiency occurs most commonly because of a combination of poor intake and inadequate synthesis. Vitamin D deficiency is defined as serum vitamin D level < 20 ng/mL.[2] It is associated with short stature, failure to thrive, respiratory infections and many other features which increase childhood morbidity. Various studies done in India have shown that the prevalence of vitamin D deficiency ranges from 70 to 100%. Studies from Delhi and Lucknow have revealed a prevalence of 93.7% and

78.3% respectively.[3,4] Many studies done previously found that supplementation with vitamin D improves growth parameters of children. Given the high prevalence of vitamin D deficiency in the pediatric age group and improvement in growth parameters following calcium and vitamin D supplementation, this study was planned to assess the role of calcium and vitamin D in improving growth parameters in the Indian children with vitamin D deficiency.

## METHODS

To ascertain the sample size, a pilot study was conducted on 10 children with vitamin D deficiency (5 in each group). One group was given 3 lac units of vitamin D (cholecalciferol) injection intramuscularly stat followed by oral vitamin D (cholecalciferol) 400 IU/day and calcium in the form of calcium carbonate (50 mg of elemental calcium/kg/day) together and the other group was given calcium in the form of calcium carbonate (50 mg of elemental calcium/kg/day) alone for 3 months. After 3 months, weight SD score of both groups were measured. The standard deviation of weight SD score of the study sample was 0.6 and difference of weight SD score between two groups was 0.35. Sample size for the present study was calculated as below: Level of significance = 5%, power = 80%,

$$n = [(Z_{\alpha/2} + Z_{\beta})^2 \times \{2(ó)^2\}] / (\mu 1-\mu 2)^2$$

Where, $ó = 0.6$ and $(\mu 1-\mu 2) = 0.35$

Based on the above formula, the sample size required per group came out to be 46.

Following that, a randomized controlled trial was conducted in community based setting in Kanpur district using multistage random sampling technique. Kanpur district consists of 10 rural blocks. Of these, one block, Vidhunu was selected using simple random sampling technique. A list of villages in block Vidhunu was obtained from the block office. Five villages were randomly selected from this list. In each of these villages, house to house survey was done and all children between 2 to 5 years who fulfilled the following all three inclusion criteria were included in the study:

- Children with vitamin D deficiency (serum vitamin D level <20ng/ml)
- Children whose parents gave consent
- Children whose parents were willing for follow up

Of the total of 395 subjects screened, 311 subjects were found to be vitamin D deficient (78.7%), 257 subjects were excluded from the study due to not meeting inclusion criteria (84 subjects were having normal Vitamin D levels, parents of 47 children did not give consent and of 14 children not willing for follow up), refusal to participate (87 subjects) and other reasons (25 subjects). A total of 138 subjects were enrolled and were divided randomly into two groups as group 1 (68 subjects) and group 2 (70 subjects) by balanced block randomization technique (Figure 1).

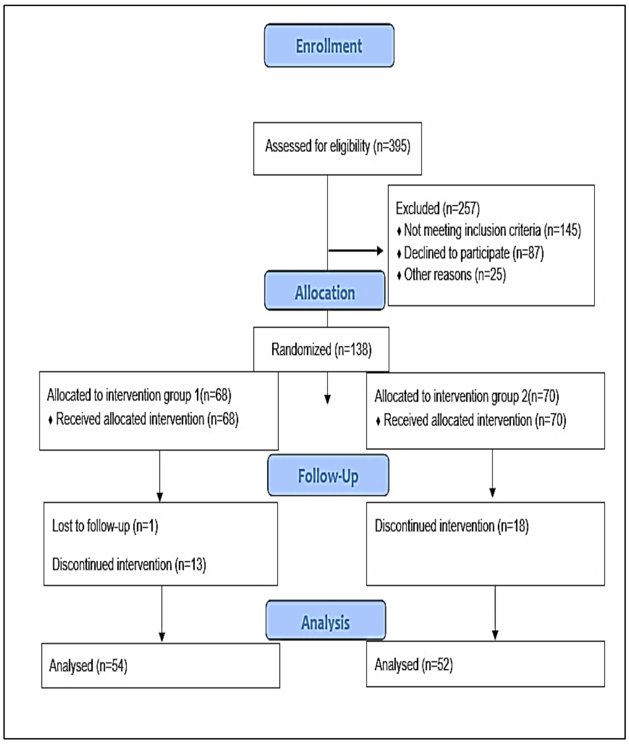


**Figure 1: Study design.**

Baseline investigations and anthropometric measurements were done by single observer. Weight of the subjects with minimal clothing was measured using electronic balance weighing scale. Standing height without shoes was measured using a stadiometer. Same scales were used for both baseline and follow up. We measured Serum 25-Hydroxyvitamin D level by radioimmunoassay. Weight and height SD score was estimated using WHO child growth standards tables (2006).[5] In Group 1, subjects were given 3 lac IU of vitamin D (cholecalciferol) intramuscularly stat followed by 400 IU/day of vitamin D (cholecalciferol) along with calcium in the form of calcium carbonate (50 mg of elemental calcium/kg/day in two divided doses) for 12 months. In Group 2, subjects were given calcium carbonate (50 mg of elemental calcium/kg/day in two divided doses) for 12 months. The local ASHAs of each of the five villages were contacted and they were made responsible for ensuring compliance in the subjects allocated to group 1 and 2. Compliance was monitored by ASHA worker by home visit once a week, supervised by investigator by telephonic communication with ASHA worker as well as family member once a week and field visit every month. At each visit ASHA worker checked empty bottles and strips. After completion of 12 months, estimation of serum vitamin D levels along with anthropometric measurements of all subjects were done by same observer. It was found that, none of the study subjects reported any adverse effects during the study period. Results of 106 subjects were analyzed to study the effect of vitamin D and calcium on growth parameters of subjects with vitamin D deficiency between 2 years to 5 years (Figure 1).

Data was analyzed using SPSS 20. Student's t test was used to analyze the differences in growth and laboratory parameters in the two groups. Multiple linear regression analysis was used to assess the effect of various factors on the growth parameters while controlling for interaction between the associated factors. Two tailed p value less than 0.05 was considered significant.

## RESULTS

In this present study, we found that out of 395 children screened, 311 had vitamin D deficiency. The prevalence of vitamin D deficiency was 78.7%. Mean age of subjects in group 1 was 40.5±9.6 months and in group 2 was 38.5±9.8 months. This difference was not found to be statistically significant (P = 0.445). Similarly, there was no statistically significant difference in baseline characteristics of group 1 and group 2 (Table 1).

**Table 1: Comparison of baseline characteristics of Group 1 and Group 2.**

| Determinant | Group 1 (n=54) | | Group 2 (n=52) | | P value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age (months) | 40.5 | 9.6 | 38.5 | 9.8 | 0.445 |
| Weight (kg) | 11.2 | 1.8 | 10.84 | 1.7 | 0.435 |
| Height (cm) | 88.5 | 6.4 | 87.4 | 6.6 | 0.521 |
| Weight SD | -2.4 | 0.8 | -2.5 | 0.7 | 0.661 |
| Height SD | -2.5 | 0.8 | -2.6 | 0.8 | 0.884 |
| Serum Vit D (ng/mL) | 13.6 | 3.5 | 13.6 | 3.3 | 0.998 |
| Serum Ca (mg/dL) | 4.6 | 0.2 | 4.5 | 0.2 | 0.075 |
| Serum ALP (units/L) | 936.0 | 498.2 | 976.0 | 527.5 | 0.778 |

Group 1: Vitamin D and Calcium supplementation; Group 2: Calcium supplementation; P value <0.05 is significant

After 12 months, the mean standard deviation score of weight of subjects of group 1 was significantly higher (-1.7±0.6) than that of subjects of group 2 (-2.3±0.6). Similarly, the mean standard deviation score of height of subjects in group 1 (-1.8±0.7) was also higher than that of subjects of group 2 (-2.4±0.7) (Table 2). This difference was found to be statistically significant. The growth velocity of subjects in group 1 was higher significantly (9.1±1.0 cm), than that of subjects in group 2 (6.9±0.6 cm). The mean vitamin D level of group 1 subjects was higher (50.3±4.3 ng/mL) than that of group 2 (17.5±3.0 ng/mL) and this difference was statistically significant. Similarly, the mean levels of serum calcium also showed significant difference (5.1±0.1 mg/dL and 4.8±0.3 mg/dL in group 1 and group 2 respectively). The mean serum alkaline phosphatase value of subjects in group 1(321.0±75.7 units/L) was lower than that group 2 (462.2±131.4 units/L). This difference was statistically significant.

**Table 2: Comparison of growth and laboratory parameters of Group 1 and Group 2 at 12 months.**

| Determinant | Group 1 (n=54) | | Group 2 (n=52) | | P value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Weight (kg) | 13.6 | 1.8 | 12.4 | 1.6 | 0.016* |
| Height (cm) | 97.7 | 6.1 | 94.3 | 6.2 | 0.06 |
| Weight SD | -1.7 | 0.6 | -2.3 | 0.6 | 0.001* |
| Height SD | -1.8 | 0.7 | -2.4 | 0.7 | 0.010* |
| Growth velocity (cm) | 9.1 | 1.0 | 6.9 | 0.6 | <0.0001* |
| Serum Vit D (ng/mL) | 50.3 | 4.3 | 17.5 | 3.0 | <0.0001* |
| Serum Ca (mg/dL) | 5.1 | 0.1 | 4.8 | 0.3 | <0.0001* |
| Serum ALP (units/L) | 321.0 | 75.7 | 462.2 | 131 .4 | <0.0001* |

Group 1- Vitamin D and Calcium supplementation; Group 2- Calcium supplementation; * P value <0.05 is significant

Multiple linear regression analysis was done taking standard deviation score of weight at 12 months as the dependent variable and factors affecting it as independent variables. R square was 90.3% (Table 3).

**Table 3: Multiple linear regression analysis of factors affecting weight standard deviation score at 12 months.**

| Factors | β coefficient | Standard error | P value |
|---|---|---|---|
| Age | 0.001 | 0.002 | 0.623 |
| Baseline WtSD | 0.772 | 0.039 | <0.0001* |
| Baseline HtSD | -0.23 | -0.034 | 0.513 |
| Supplementation (1=vitamin D with calcium, 0=calcium alone) | 0.522 | 0.043 | <0.0001* |

R square= 90.8%; *P value <0.05 is significant

It was observed that the standard deviation score of weight at 12 months was significantly associated with baseline weight SD score (p <0.0001) and supplementation with vitamin D and calcium (p<0.0001). The β coefficient for baseline weight SD score was 0.772 and for supplementation with vitamin D and calcium was 0.522. Similarly, multiple linear regression analysis was done taking standard deviation score of height at 12 months as the dependent variable and factors affecting it as independent variables. R square was 95.6% (Table 3). It was observed that the height SD score at 12 months was significantly associated with baseline height SD score (p <0.0001) and supplementation with vitamin D and calcium (p <0.0001). The β coefficient for baseline height SD score was 0.869 and for vitamin D was 0.532.

**Table 4: Multiple linear regression analysis of factors affecting height standard deviation score at 12 months.**

| Factors | β coefficient | Standard error | P value |
|---|---|---|---|
| Age | 0.000 | 0.002 | 0.882 |
| Baseline WtSD | 0.027 | 0.031 | 0.382 |
| Baseline HtSD | 0.869 | 0.027 | <0.0001* |
| Supplementation (1=vitamin D with calcium, 0=calcium alone) | 0.532 | 0.034 | <0.0001* |

R square= 95.6%; *P value <0.05 is significant

## DISCUSSION

In the present study, the community based prevalence of vitamin D deficiency was 78.7%. This was similar to various studies done previously. Marwaha et al observed vitamin D deficiency of 93.7% in school girls between 6 years to17 years.[3] In a Lucknow based study, Arya et al found vitamin D deficiency of 78.3% in the adult population.[4] Khadgawat et al, Garg et al and various other studies have also reported a high prevalence of vitamin D deficiency in Indian population.[6-13]

In the present study, we found that after supplementation with vitamin D, the weight SD score of children increased significantly. This is due to direct influence of vitamin D levels on weight of the children. Tom TD et al have also reported that supplementation with vitamin D improves the weight of children.[14] In the present study, height SD scores and growth velocity also improved significantly with vitamin D supplementation. Gupta R et al also found that cholecalciferol and calcium supplementation results in enhanced skeletal muscle strength and physical performance.[15]

In the present study, we administered mega dose of vitamin D (3 lac IU) and found significant improvements in vitamin D levels and growth of children. Similarly, Billooa et al demonstrated that with the one dose of vitamin D, there was appreciable gain of weight and height during follow up.[16] Hackman KL et al, also showed that injectable high-dose regimen may be an effective and cheap alternative for patients with vitamin D deficiency.[17]

Cesur Y et al showed that 150,000 IU or 300,000 IU of vitamin D was adequate in the treatment of vitamin D deficiency, but 600,000 IU of vitamin D may carry the risk of hypercalcemia.[18] Gordon CM et al demonstrated that giving high dose vitamin D supplementation is essential to increase vitamin D level in children. This is probably due to higher compliance for single dose when compared to daily dose. Marwaha RK et al also found that supplementation with vitamin D resulted in a significant increase in serum 25(OH)D levels in vitamin D deficient children.[19] In a similar study, Soliman AT et al, also found that an IM injection of a mega dose of cholecalciferol is a safe and effective therapy for treatment of vitamin D deficiency rickets in infants and toddlers with normalization of all the biochemical parameters and healing of radiological manifestations.[20] Tom TD et al also found that final serum vitamin D level was higher in the group that received both calcium and vitamin D than in the group which received calcium alone.[21]

In the present study, we supplemented a mega dose of 3,00,000 IU IM stat to correct vitamin D deficiency followed by an oral dose of 400 IU daily for 12 months and found significant improvement in the weight SD score of the study subjects. A daily dose of 400 IU is recommended by both American Academy of Pediatrics and ICMR for children less than 1 year as prophylaxis against vitamin D deficiency.[22] In the present study, we found a high prevalence of vitamin D deficiency among children between 2 years to 5 years also. So, we recommend supplementation of vitamin D to all children till 5 years of age as it improves weight SD score and can be used as primary prevention of malnutrition which is an important indirect cause of childhood morbidity and mortality.

Routine vitamin A supplementation is recommended by World Health Organization in infants and children of 6-59 months of age as a public health intervention to reduce the risk of all-cause mortality.[23] This policy is being followed in India under the RCH 2 program. Vitamin D supplementation has also been recommended by American Academy of Pediatrics for all children till adolescence.[24] There is a high prevalence of vitamin D deficiency in the 2 to 5 years age group as observed in the present study, so we recommend that regular supplementation of all children vitamin D and this can be considered as a policy for prevention of malnutrition.

## CONCLUSION

Vitamin D supplementation along with calcium improves the growth of children. Regular supplementation of all children with vitamin D can be considered as a policy for prevention of malnutrition

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