Original Research Article

Correlation of vitamin D level with its related biochemical parameters and impact of different treatment regimens on their correction

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ABSTRACT

Background: Vit D is a fat-soluble vitamin that is produced when ultraviolet rays from sunlight strike the skin and trigger vit D synthesis. Aims and Objectives of the study were to find out the correlation of vit D level with its related biochemical parameters and impact of two different treatment regimens on their correction.

Methods: A total of 107 patients were followed up out of which 89 were vit D deficient and rest were vit D insufficient.

Results: Mean age of the patients was 6.11±4.49 and males comprised 66%. Mean BMI of children included in group A, B and C was 19.40±2.69, 19.60±3.18 and 20.95±3.72 kg/m² respectively. Vit D levels at baseline had a significant inverse correlation with ALP (r=-0.27, p value=0.008). Before and after comparison of mean serum calcium levels revealed significant improvement in both the treatment groups. Severity of vit D deficiency, at baseline, 9.10, 77.30 and 13.60% of patients had vit D levels of less than 5, 5 to 15 and more than 15 for group A respectively. In group B at baseline, 6.70, 71.10 and 22.20% of patients had vit D levels of less than 5, 5 to 15 and more than 15 respectively.

Conclusions: Present study found that 60,000 IU/week and dose of 2000 IU/day for infants or 5000 IU/day for 1 to 18 years of age, along with 500 to 800 mg oral calcium for 6 to 8 weeks can result in correction of vit D deficiency.

Keywords: Vit D, Biochemical parameters, Treatment regimes

INTRODUCTION

Vit D is a fat-soluble vitamin that is produced when ultraviolet rays from sunlight strike the skin and trigger vit D synthesis. Soranus, a Roman physician in the 1st and 2nd century AD is often credited as one of the early describers of some rickets deformities. Soranus attributed these changes to inappropriate maternal hygiene and lifestyle.1 Whistler described the rickets skeleton as poorly mineralized and deformed while professor Glisson provided a detailed published description.2 During that period, rickets was endemic in England. Known as ‘the English disease’, it was explained by the population’s urbanization.3 However, the mystery of nutritional vit D deficiency and its relationship with rickets was solved by sir Edward Mellanby in 1920 through an experimental demonstration and dietary manipulation of captive dogs.4

The vit D from skin synthesis or digestive tract enters the blood circulation and is hydroxylated by a specific enzyme forming 25-hydroxyvitamin D (25(OH)D) in the liver. 25(OH)D is the main circulating form of vit D in the body.5 The best-known skeletal action for the active form of vit D involves regulating both bone formation and resorption, as enacted through osteoclastic and osteoblastic cell lineages.6,7 In India, Marwaha et al reported high prevalence of severe vit D deficiency in adolescent males (27%) and females (42%).8

There is a plethora of literature on vit D deficiency and its treatment and multiple guidelines have been suggested.
by various international bodies. However, a lack of consensus about the ranges for deficiency and sufficiency and peculiarities of the Indian circumstances, results in confusion for a pediatrician treating vit D deficiency. Therefore, the present study was conducted to assess and compare the clinical outcomes of patients of vit D deficiency treated by two different vit D and calcium supplementation regimes.

**METHODS**

This randomized controlled study was conducted at department of pediatrics at Fortis Escorts hospital, Faridabad from January 2019 to December 2019. Patients were included in the study after taking an informed consent.

Children and adolescent patients investigated for low vit D levels with its related biochemical parameters by the clinician on clinical or radiological ground visiting outpatient clinic or inpatient ward were chosen for the study. All children and adolescent patients aged 1 month to 18 years with low serum 25(OH)D level who presented to our department during the study period were included.

Children having vit D deficiency rickets, associated with underlying disease, such as fat malabsorption, liver disease, renal insufficiency and those receiving total parenteral nutrition, previously diagnosed vit D deficiency secondary to congenital disorders of vit D metabolism including 1 alpha hydroxylase deficiency (pseudo-vitamin D deficiency rickets) and phosphopenic rickets where hypophosphatemia is the primary cause of rickets were excluded from the study.

Lab investigation prior to treatment such as serum calcium, serum phosphate, serum PTH, Serum vit D level, alkaline phosphatase (ALP) and X-ray of left wrist were carried out, when required.

**Selection of patients**

The patients were divided into three groups-A, B and C. Group A included 44 patients (daily regime), group B included 45 patients (weekly regime) having vit D deficiency and group C included 18 patients having vit D (insufficient). Present study employed block randomization technique regarding selection of patients. In this technique, blocks of size four, i.e. for every four vit D deficient patients randomized two received daily vit D supplement and other two received weekly vit D supplement. There were six different ways that four patients can be split evenly between two treatments: AABB, ABAB, ABBA, BAAB, BABA and BBAA. To randomly select among these six different blocks, random number generating function RANDBETWEEN () was used with lower limit as 1 and upper limit as 6. Blocks were created according to the generated number, for instance if 5 is generated then BABA sequence was used and so on. In this way patients were randomized to receive the treatment.

**Data collection**

Patients fulfilling the inclusion criteria, were taken up for the study. Serum vit D level done in children decided by clinician by standard method like chemiluminescence method were considered for comparing. At the time of enrolment in the study, the following investigations were observed:

- Serum calcium (mg/dl) (spectrophotometry): 8.8-10.8, serum phosphorus (mg/dl) (spectrophotometry): 4.0-7.0, serum alkaline phosphatase (IU/L) (spectrophotometry): 44-147, serum parathormone level (chemiluminescence): 18.4-80.1 and serum 25(OH)D level (ng/dl) (chemiluminescence):
  - Deficient <20, insufficient-20-30, sufficient-30-100, toxic >100.

According to US endocrine society criteria all patients having normal and low vit D levels are classified as: Normal vit D levels (≥30 ng/ml), insufficient (21 to 29 ng/ml) and deficient (<20 ng/ml).

The following intervention was done in vit D deficient patients:

**Table 1: Oral vitamin D supplementation regimes for group A and group B.**

| Oral vit D supplement* | Group A (daily regime) IU/day | Group B (weekly regime) IU/week | Calcium supplementat ion (mg/day oral) |
|-----------------------|-------------------------------|--------------------------------|--------------------------------------|
| 6 weeks               | 2000                          | 60,000                         | 500                                  |
| 6 weeks               | 5000                          | 60,000                         | 600-800                              |

Oral calcium (calcium phosphate) in liquid form (syrup Calcimax-P). *Oral vit D (cholecalciferol) in liquid form (syrup Vit D3 nano shots/drops D3 Must).

After initiating treatment, patients were followed up for 6 to 8 weeks, after which the above-mentioned laboratory investigations were repeated.

The data was analyzed by using statistical package for social sciences (SPSS) version 21.0. Categorical variables presented as number and percentage (%) and continuous variables as mean ± SD or median. Normality of data was tested by Kolmogorov-Smirnov test. Quantitative variables were compared using paired t-test. Qualitative variables were analyzed using chi-square /Fisher’s exact test. A p<0.05 was considered statistically significant.

**RESULTS**

Mean age of the patients included in the study was 6.11±4.49. Among group A, B and C, the mean age of the
patients was 4.91±4.05, 6.49±4.53 and 8.13±4.76 years respectively (p<0.05). In group A males comprised 66% and in group B males comprised 64% of their group. Mean weight of the children included in group A, B and C was 19.40±2.69, 20.95±3.72 and 22.31±12.34 kg/m² respectively. Mean height of children included in group A, B and C was 103.81±26.41, 112.44±28.15 and 123.97±33.26 cm respectively. Mean BMI of children included in group A, B and C had their ALP levels above 147. After treatment, the difference was statistically not significant (p=0.08).

Table 3: Comparing mean serum phosphate levels in treatment group A and B at baseline and after treatment and before and after treatment as well.

| Phosphate (mg/dl) | Intervention | A    | B    | Mean diff* | P*   |
|-------------------|--------------|------|------|------------|------|
| Baseline          |              | 4.79 | 4.85 | 0.06       | 0.76 |
| After treatment   |              | 5.39 | 5.4  | 0.006      | 0.96 |
| Mean diff**       |              | 0.6  | 0.55 |            |      |
| P***              |              | <0.001 <0.001 |      |      |

Bone pain was the most common presenting complaint in the study population (48%). General body pain and recurrent infections were the next most common presenting complaints in the present study (48% and 45% respectively).

Table 2: Comparing mean serum calcium levels in treatment group A and B at baseline and after treatment and before and after as well.

| Calcium (mg/dl) | Intervention | A        | B        | Mean diff* | P*   |
|-----------------|--------------|----------|----------|------------|------|
| Baseline        |              | 8.71±0.87| 8.98±0.73| 0.26       | 0.12 |
| After treatment |              | 9.38±0.73| 9.69±0.96| 0.3        | 0.09 |
| Mean diff**     |              | 0.67     | 0.71     |            |      |
| P***            |              | <0.001   | <0.001   |            |      |

Serum vit D levels at baseline had a positive correlation with serum calcium and phosphate; though both were statistically not significant. With ALP the vit D levels were significantly inversely correlated (r =-0.27, p=0.008) and with PTH also vit D levels were inversely correlated, though not significantly (r=-0.16, p=0.11).

Table 4: Comparing mean serum ALP levels in treatment group A and B at baseline and after treatment and before and after treatment as well.

| ALP (IU/L) | Intervention | A        | B        | Mean diff* | P*   |
|------------|--------------|----------|----------|------------|------|
| Baseline   |              | 293.70±71.37| 281.11±73.68| -12.59     | 0.41 |
| After treatment |          | 230.52±61.0  | 214.91±53.32 | -15.61     | 0.2 |
| Mean diff**|              | -63.18    | -66.2    |            |      |
| P***       |              | <0.001    | <0.001   |            |      |

Mean serum ALP levels were found to be similar in the two treatment groups at baseline and after treatment. Before and after comparison of mean serum ALP levels revealed significant decrease in both the treatment groups (mean difference for group A=-63.18, p<0.001; for group B=-66.2, p<0.001).

Table 5: Comparing mean PTH levels in treatment group A and B at baseline and after treatment and before and after treatment as well.

| PTH (pg/ml) | Intervention | A        | B        | Mean diff* | P   |
|------------|--------------|----------|----------|------------|-----|
| Baseline   |              | 53.73±22.07| 37.72±21.15| -16.01     | 0.4 |
| After treatment |          | 30.55±11.85 | 29.18±10.65 | -1.37      | 0.79|
| Mean diff**|              | -23.18    | -8.54    |            |     |
| P***       |              | <0.001    | <0.005   |            |     |

Before and after comparison of mean serum calcium levels revealed significant improvement in both the treatment groups (mean difference for group A=0.67, p<0.001; for group B=0.71, p<0.001).

After treatment all patients in group A had serum phosphate levels 4 to 7, while in group B 11% had levels below 4 (p=0.029).

Before and after comparison of mean serum phosphate levels revealed significant improvement in both the treatment groups (mean difference for group A=0.6, p<0.001; for group B=0.55, p=0.001).

At baseline all patients in the two treatment groups had their serum ALP levels above 147. After treatment, 4.5% in group A and 15.6% in group B had their ALP levels 44 to 147, though the difference was statistically not significant (p=0.08).
Mean serum PTH levels were found to be similar in the two treatment groups at baseline and after treatment. Before and after comparison of mean serum PTH levels revealed significant decrease in both the treatment groups (mean difference for group A=−23.18, p<0.001; for group B=−8.54, p<0.001).

At baseline all patients in the two treatment groups had their serum vit D levels less than 20. After treatment, 86.40% and 75.60% of the patients had vit D level >30, 11.40 and 20.00% had vit D level 20 to 30 and only 2.30 and 4.40% still had vit D less than 20 in group A and B respectively. However, the distribution of patients according to their vit D levels in the two treatment groups was similar.

Table 6: Comparing mean serum vit D levels in treatment group A and B at baseline and after treatment and before and after treatment as well.

| Vit D (ng/ml) | Intervention | A | B | Mean diff* | P* |
|--------------|--------------|---|---|------------|----|
| Baseline     |              | 11.28±4.30 | 11.78±3.96 | 0.49 | 0.57 |
| After treatment | 34.19±5.61 | 33.84±6.61 | -0.35 | 0.78 |
| Mean diff** | 22.91        | 22.06        | <0.001 | <0.001 |

*comparing group, A vs group B (student's t test); **comparing pre and post within a treatment group (paired t test)

Mean serum vit D levels were found to be similar in the two treatment groups at baseline and after treatment (11.28±4.30 vs 11.78±3.96, p=0.57 at baseline and 34.19±5.61 vs 33.84±6.61, p=0.78 after treatment). Before and after comparison of mean serum vit D levels revealed significant decrease in both the treatment groups (mean difference for group A=22.91, p<0.001; for group B=22.06, p<0.001).

On comparing the severity of vit D deficiency, at baseline, 9.10, 77.30 and 13.60% of the patients had vit D levels of less than 5, 5 to 15 and more than 15 for group A respectively. In group B at baseline, 6.70, 71.10 and 22.20% of the patients had vit D levels of less than 5, 5 to 15 and more than 15 respectively. The distribution of patients was statistically not significant. After treatment all patients in both the treatment groups were found to have vit D levels between 15 to 20.

We observed that 18 patients had radiological evidence of bony defects. None of the biochemical parameters at baseline were found to have a significant association with radiological evidence of bony defects.

Group C patients had vit D insufficiency and were not given any specific treatment. Among group C patients, 39% had serum calcium below 8.8 at baseline, which increased to 44% at the end of the study. Serum PTH levels were <18.4 in 17% at baseline, which reduced to 6% at the end of the study. At the end of the study, vit D levels were >30, 20 to 30 and <20 in 22%, 44 and 33% respectively.

Table 7: Comparing mean levels of various biochemical parameters at baseline and at the end of the study for group C.

| Variables                  | Mean     | Std. Dev | P     |
|---------------------------|----------|----------|-------|
| Serum calcium (mg/ml)     | At baseline (n=18) | 8.867 | 0.663 | 0.38 |
|                           | At end of study (n=18) | 9.15 | 1.1168 | |
| Serum phosphate (mg/ml)   | At baseline (n=18) | 5.078 | 0.6217 | 0.59 |
|                           | At end of study (n=18) | 5.006 | 0.5955 | |
| Serum ALP (IU/L)          | At baseline (n=18) | 314.11 | 63.682 | 0.41 |
|                           | At end of study (n=18) | 302.22 | 83.6136 | |
| Serum PTH (pg/ml)         | At baseline (n=18) | 32.38 | 15.8205 | <0.01 |
|                           | At end of study (n=18) | 37.42 | 15.0924 | |
| Serum vit 25(OH)D-1 (ng/ml) | At baseline (n=18) | 24.65 | 2.8572 | 0.52 |
|                           | At end of study (n=18) | 23.76 | 7.8388 | |

Analyzed by student’s t test

In group C patients, mean serum calcium, phosphate, ALP and vit D levels were similar at baseline and at the end of the study. However, serum PTH levels were found to increase significantly from 32.389 to 37.422 at baseline and at the end of the study respectively.

**DISCUSSION**

Recent years have witnessed an increased interest in vit D status and potential impact of deficiency/insufficiency in various disease states. More recently, investigations have focused on clinical benefits of therapeutic supplementation with vit D. These studies are pertinent, especially in India as despite the presence of abundant sunshine in India, high prevalence of vit D deficiency/insufficiency is reported.

Mean age of the patients included in the study was 6.11±4.49 years. Among group A, B and C, the mean age of the patients was 4.91±4.05, 6.49±4.53 and 8.13±4.76

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He two treatment groups were comparable in the two treatment groups, especially when they were Indian families, especially when they were compared. After 20 years to three groups; group A (n=70) received 50,000 U oral cholecalciferol monthly (equal to 1600 U per day), group B (n=70), 50,000 U bimonthly (equal to 800 U/day) and group C (n=70), placebo for 6 months. In their study, mean age of the population was 16.3±1.3 years, a significantly greater proportion of girls were in the vit D deficiency group, and the mean serum vit D level was significantly lower in girls than boys.

We observed mean BMI of children included in Group A, B and C was 19.40±2.69, 19.60±3.18 and 20.95±3.72 kg/m² respectively. Majority of the children had a BMI of 18.5 to 24.9 kg/m². It is known that in obesity there is a sequestration of part of vit D in adipose tissue and, in fact, some researchers have observed a relation between overweight and vit D deficiency in infants and children. Effect of obesity on response to vit D supplementation in vit D deficiency was studied by Motlaghzadeh et al. They revealed that the response to vit D supplementation was almost 2-fold lower in the obese group compared with the non-obese one.

In the present study, though serum vit D levels at baseline had a positive correlation with serum calcium and phosphate; both were statistically not significant. With ALP the vitamin D levels were significantly inversely correlated (r=-0.27, p=0.008) and with PTH also the vit D levels were inversely correlated, though not significantly (r=-0.16, p=0.11). Choi et al found that serum 25(OH)D level had a positive relationship with serum calcium and phosphorus.

Similar to our study, Gordon and colleagues compared the safety and efficacy of 2000 IU vit D2 daily, 50,000 IU vit D2 weekly, and 2000 vit D3 daily among infants and toddlers. They observed the mean change in serum calcium levels was small and comparable in the three treatment groups (3% for vit D2 daily, 3% vit D2 weekly, 1% vit D3 daily).

In the present study it is observed that at baseline the distribution of patients in the two treatment groups according to their serum phosphate levels were comparable. After treatment all patients in group A had serum phosphate levels 4 to 7, while in group B 11% had levels below 4 (p=0.029). Mean serum phosphate levels were found to be comparable in the two treatment groups at baseline and after treatment. Before and after comparison of mean serum phosphate levels revealed significant improvement in both the treatment groups (mean difference for group A=0.6, p<0.001; for group B=0.55, p<0.001). Gordon and colleagues also demonstrated similar increase in serum phosphate levels with weekly or daily regimens of vit D supplementation, with no significant difference in the effective of the supplementations.

In the present study, all patients in our two treatment groups had their serum ALP levels above 147 at baseline. After treatment, 4.5% in group A and 15.6% in group B had their ALP levels 44 to 147, though the difference was statistically not significant (p=0.08). Mean serum ALP levels were found to be comparable in the two treatment groups at baseline and then after treatment and both groups showed significant decrease. Gordon et al found no significant impact of treatment on alkaline phosphatase concentrations.

Mean serum PTH levels were found to be comparable in the two treatment groups at baseline and then after treatment and both groups showed significant decrease as well (greater decrease in group A). Gordon et al also found that all cases returned to normal PTH limits after treatment. The largest change in PTH was observed in the group receiving vit D2 weekly (down 40%, from 32.1 to 19.2 pg/ml, adjusted for covariates), compared with patients in the other treatment arms (vit D2 daily, down 20% from 38.5 to 30.8 pg/ml, and vit D3 daily, down 36% from 40.9 to 26.3 pg/ml). There was no significant difference in PTH suppression among the three groups.

At baseline all patients in the two treatment groups in the present study had their serum vit D levels less than 20. After treatment, 86.40% and 75.60% of the patients had vit D level >30, 11.40% and 20.00% had vit D level 20 to 30 and only 2.30 and 4.40% still had vit D less than 20 in group A and B respectively. However, the distribution of patients according to their vit D levels in the two treatment groups were comparable. Mean serum vit D levels were found to be comparable in the two treatment groups at baseline and after treatment. The fact that the serum 25(OH)D level normalized in most study subjects also indicates that impaired 25-hydroxylation is not involved in the etiopathogenesis of subnormal 25(OH)D levels in Asian Indians. The pattern of rise in serum 25(OH)D with cholecalciferol and calcium supplementation and associated normalization of serum PTH levels observed in the current study is similar to that observed earlier in Caucasian subjects. There is limited literature in which different doses of vit D have been used to achieve the desired level of 25(OH)D. Ghazi et al found that with both monthly and bimonthly vit D supplementation, mean 25(OH)D increased from 32±22 to 60±27.5 and 28.25±14.5 to 45.75±24. However, the increase was more with monthly schedule. These were unlike the results of the present study where daily and weekly regimes effect were not significantly different but showed a trend favoring daily regime. This was coupled with cost advantage of daily regime and probably better compliance may be favored it over weekly regime.

The cost and convenience of daily vit D supplements may be prohibitive in some Indian families, especially when needed for several children in the same family for prolonged periods. It is also important to provide education about vit D, risk factors for low vit D, and sun protection and exposure, and to encourage regular outside
play and physical activity. A meta-analysis by Iglay et al found that weekly dosing was associated with better adherence levels and greater odds of being adherent compared with daily dosing in patients with osteoporosis.\textsuperscript{14} As for adherence to vit D supplements, no relevant results could be found regarding the compliance to the therapy, however poor adherence to daily dosing of medications and supplements is reported.

**CONCLUSION**

The present study found that 60,000 IU/week and dose of 2000 IU/day for infants or 5000 IU/day for 1 to 18 years of age, along with 500 to 800 mg oral calcium for 6 to 8 weeks can result in correction of vit D deficiency. Moreover, present study also observed a similar significant increase in serum calcium, phosphate and a decrease in alkaline phosphatase and parathyroid hormone with both treatment regimes. These results indicate that pediatricians can determine the appropriate method of treatment for a given patient or family to ensure compliance, given that no difference in efficacy or safety was noted.

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**REFERENCES**

1. Dunn PM. Soranus of Ephesus (circa AD 98-138) and perinatal care in Roman times. Arch Dis Child. 1995;73:51-2.  
2. Glisson F. A treatise of the rickets: being a disease common to children, Culpeper N, translated and edited (London): P Cole. 1651.  
3. Dunn PM. Glisson F. (1597-1677) and the “discovery” of rickets. Arch Dis Child. 1998;78:154-5.  
4. Mellanby E. An experimental investigation on rickets 1919. Nutrition. 1989;5:81-6.  
5. Ko SH. Dietary calcium and 1,25-dihydroxyvitamin D3 regulate transcription of calcium transporter genes in calbindin-D9k knockout mice. J Reprod Dev. 2009;55:137-42.  
6. Suda T. Vitamin D and bone. J Cell Biochem. 2003;88:259-66.  
7. Atkins GJ, Anderson PH, Findlay DM, Welldon KJ, Vincent C, Zanettino AC et al. Metabolism of vitamin D3 in human osteoblasts: evidence for autocrine and paracrine activities of 1 alpha, 25-dihydroxyvitamin D3. Bone. 2007;40:1517-28.  
8. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA et al. IOF Committee of Scientific Advisors (CSA) Nutrition Working Group. Global vitamin D status and determinants of hypovitaminosis D. Osteopor Int. 2009;20:1807-20.  
9. Marwaha RK, Tandon N, Reddy DR, Aggarwal R, Singh R, Sawhney RC et al. Vitamin D and bone mineral density status of healthy schoolchildren in northern India. Am J Clin Nutr. 2005;82:477-82.  
10. Ghazi AA, Hosseinpanah FE, Ardakani EM, Ghazi S, Hedayat M, Azizi F. Effects of different doses of oral cholecalciferol on serum 25 (OH) D, PTH, calcium and bone markers during fall and winter in schoolchildren. Eur J Clin Nutr. 2010;64:1415.  
11. Motlaghzadeh Y, Sayarifard F, Allahverdi B, Rabbani A, Setoodeh A, Azadeh S et al. Assessment of Vitamin D status and response to vitamin d3 in obese and non-obese Iranian children. J Trop Pediatr. 2016;62:269-75.  
12. Choi JH, Lee B, Lee JY, Kim CH, Park B, Kim DY et al. Relationship between sleep duration, sun exposure, and serum 25-Hydroxyvitamin D status: a cross-sectional study. Scientific Rep. 2020;10:4168.  
13. Gordon CM, Williams AL, Feldman HA, May J, Sinclair L, Vasquez A et al. Treatment of hypovitaminosis D in infants and toddlers. J Clin Endocrinol Metab. 2008;93:2716-21.  
14. Iglay K, Cao X, Mavros P, Joshi K, Yu S, Tunceli K. Systematic Literature Review and Meta-analysis of Medication Adherence with Once-weekly Versus Once-daily Therapy. Clin Therap. 2015;37:1813-21.

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