

**Original Article:****Vitamin D supplementation therapy – comparison of efficacy of three different protocols**C.V. Harinarayan,<sup>1</sup>P.M. Srinivasa,<sup>2</sup> K. Thennarasu,<sup>3</sup> A. Leena<sup>4</sup>*Department of<sup>1</sup> Endocrinology, Diabetes and Osteoporosis, Institute of Endocrinology, Diabetes and Osteoporosis, Sakra World Hospitals, Bengaluru and Departments of<sup>2</sup> Endocrinology,<sup>4</sup> Clinical Biochemistry, Fortis Hospitals, Bengaluru and Department of<sup>3</sup> Biostatistics, National Institute of Mental Health and Neuro Sciences, Bengaluru***ABSTRACT****Background:** To study the efficacy of vitamin D supplementation therapy with three different protocols.**Methods:** In protocols 1 (intensive) and 3 (standard) oral cholecalciferol was given 60,000 IU/week/8 weeks followed bimonthly for 12 weeks. In protocol 2 parenteral-bolus cholecalciferol was given as 600,000 IU loading dose, 8 weeks later followed by cholecalciferol 60,000IU bimonthly for 12 weeks. Elemental calcium (1 g/day) was administered for full duration of study in all three protocols. Serum albumin, calcium, phosphorous, alkaline phosphatase, 25-hydroxy vitamin D (25OHD) and parathyroid hormone were tested at baseline, at 2<sup>nd</sup>, and 5<sup>th</sup> months. Statistical analysis was performed using random measures analysis of variance. As patients receiving protocol 3 were significantly older compared to the other two groups, age-adjusted analysis was carried out.**Results:** Intention-to-treat and per-protocol analysis showed that patients receiving protocol 2 had achieved 25OHD sufficiency levels at 8 weeks suggesting that protocol 2 appeared to perform best among the three protocols. However, these differences were not sustained at 5 months suggesting the need for continuing supervision.**Conclusions:** Despite varied responses of different biochemical markers, all three protocols were effective in bringing up 25OHD levels. However, protocol 2 performed the best among the three protocols. Our observation also highlight the importance of need for ongoing supplementation and continuing supervision of the same.**Key words:** *Vitamin D, Dietary supplement.***Harinarayan CV, Srinivasa PM, Thennarasu K, Leena A. Vitamin D supplementation therapy – comparison of efficacy of three different protocols. J Clin Sci Res 2015;4:273-80. DOI: <http://dx.doi.org/10.15380/2277-5706.JCSR.15.025>****INTRODUCTION**

Despite a sunny environment, hypovitaminosis D is common in India.<sup>1</sup> Among apparently healthy Indian subjects residing in India, more than 90% have been observed to have subnormal serum 25-hydroxy vitamin D (25OHD) levels. During winters, their 25OHD values are almost undetectable.<sup>2</sup> Of these, 20% also revealed evidence of parathyroid hyperactivity.<sup>3,4</sup> Inadequate exposure to sunshine and skin pigmentation are thought to be responsible for hypovitaminosis D in them.<sup>2</sup> Evidence is also available suggesting that

improving vitamin D status has beneficial effects and may reduce health care expenditure for many chronic diseases.<sup>5</sup>

However, inspite of abundant evidence available regarding the importance of vitamin D in general health and reliable data on widespread occurrence of vitamin D deficiency, little data are available regarding treatment of this condition. Cholecalciferol (D<sub>3</sub>) and ergocalciferol (D<sub>2</sub>) are equally effective in raising 25OHD levels.<sup>6</sup> It has been observed that the conventionally administered supplements are inadequate even for

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prevention; much higher doses are required for treatment of vitamin D deficiency. Compliance with oral vitamin D replacement therapy has been found to be low.<sup>7-9</sup> Further, only 50% of postmenopausal women with osteoporosis who are advised calcium and/or vitamin D have been observed to have adhered to treatment.<sup>7</sup> The pharmacokinetics, biochemical effects, efficacy and safety of a single high-dose oral or injectable cholecalciferol has been evaluated and found to be effective safe, and well tolerated.<sup>10-14</sup>

There are several unanswered questions regarding the use of different pharmaceutical forms of vitamin D. Because of lack of head-to-head comparative studies, it is unclear whether treatment given orally or by injection would be better effective. In order to provide answer to these uncertainties, we carried out head-to-head comparison of same dosage of vitamin D administered by oral and injectable routes of treatment, in achieving normal serum 25OHD level, and assess various other biochemical parameters that support adequacy of serum vitamin D levels. We also aimed to see if intensive monitoring of oral therapy encouraging adherence to treatment would ensure better result in achieving desired therapeutic levels compared to standard treatment.

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## MATERIAL AND METHODS

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All subjects residing in the place of study were studied during the period July to December 2013. Subjects with history of diabetes mellitus, renal and liver diseases, patients known to have hypocalcaemia, hypercalcaemia or hyper-parathyroidism, pregnant and lactating women, history of drug ingestion (like corticosteroids, anti-epileptic drugs, anti-tuberculosis drugs, especially rifampicin) and those with granulomatous diseases were excluded from the study. Written informed consent was obtained from all participants. The study was approved by the Institutional Review Board.

In all subjects peripheral venous blood samples were obtained and serum creatinine, albumin, calcium, phosphorus, alkaline phosphatase, 25OHD and parathyroid hormone (PTH) concentrations were measured. Quantitative estimation of serum albumin, creatinine, calcium, phosphorus, alkaline phosphatase was done using Roche Cobas analyzers (Cobas, Roche diagnostics Ltd, Rotkruez, Switzerland) with their respective kits. Serum 25OHD concentrations were measured by competitive radioimmuno assay (DiaSorin, Stillwater, MN, USA, Catalogue No 68100E). Intact PTH was estimated by electro-chemiluminescence (ECLIA) on Elecsys 2010 Roche Cobas kit (Roche diagnostics Indianapolis). The normal values in serum for the parameters tested were: creatinine 0.7-1.4 mg/dL; albumin 3.5-5.2 g/dL; calcium 8.5-10.2 mg/dL; phosphorus 2.7-4.5 mg/dL; and alkaline phosphatase 40-130 IU/L. A 25OHD value greater than 30 ng/mL was defined as vitamin D sufficiency; a value less than 20 ng/mL was defined as vitamin D deficiency; and a value greater than 30 ng/mL was defined as sufficiency.<sup>15</sup> A PTH value of 15-65 pg/mL was considered normal as per the kit manufacturer.

Vitamin D supplementation along with elemental calcium was done in three different protocols. Protocol 1 (intensive regimen) consisted of oral cholecalciferol 60,000 IU (D-Rise,<sup>®</sup> US Vitamins Ltd, Mumbai, India) administered once a week for two months along with oral supplementation of elemental calcium (1 g/day) [Calcitab<sup>®</sup> (Intas Pharmaceuticals, Dehradun, Uttaranchal, India), each tablet containing 1250 mg of calcium carbonate (equivalent to 500 mg elemental calcium) and 500 IU cholecalci fenol Vitamin D supplementation was supervised for every dose. A day prior and on the day of scheduled supplementation of vitamin D a reminder was sent to each patient through short-message service (SMS) and patients were also reminded through their mobile phones. Supplementation of calcium

was supervised by periodic SMS and telephonic interaction. After two months of therapy, cholecalciferol was supplemented orally in a dosage of 60,000 IU per fortnight along with supplementation of elemental calcium 1 g/day, for a period of three months.

In protocol 2 (parenteral regimen), cholecalciferol 600,000 IU was administered as a single dose, intramuscular injection, (injection Arachitol<sup>®</sup>, Abbott Pharmaceuticals, Sarkhej, Ahmedabad, Gujarat, India), along with supplementation of elemental calcium 1 g/day. After two months of therapy, cholecalciferol was supplemented orally at 60,000 IU per fortnight along with supplementation of elemental calcium 1 g/day for a period of three months.

In protocol 3 (standard regimen), the supplementation was similar to protocol 1, except that there was no supervised monitoring by periodic SMS and telephonic interactions.

The tolerable upper level intake (UL) of cholecalciferol advocated by Endocrine Society Clinical Practice Guidelines for vitamin D supplementation<sup>15</sup> was 10,000 IU/ day of cholecalciferol for adults, who are vitamin D deficient, for a period of eight weeks. All subjects were observed for adverse effects of excess vitamin D supplementation, namely, symptoms of hypercalcaemia like polyuria, polydipsia, vomiting, fatigue, anorexia, weakness, weight loss, graveluria and decreased appetite.

### Statistical analysis

Statistical analysis was done using statistical software Statistical Package for Social Sciences (SPSS) (version 15.0; SPSS Inc, Chicago, IL, USA) and Stata Version 12.1 (Stata Corp, Texas, USA). Descriptive results are presented as mean  $\pm$  SD. A age-adjusted comparison of efficacy of treatment between three protocols was performed using random measures analysis of variance (RMANOVA), Intention to treat

(ITT) analysis based on last observation carried forward (LOCF) and per-protocol analysis were done. A p-value less than 0.05 was considered statistically significant.

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## RESULTS

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The demographic characteristics, various analytes at recruitment, and at the end of 2<sup>nd</sup> and 5<sup>th</sup> month of supplementation are shown in Table 1. Patients receiving protocol 3 were significantly older. As there was a statistically significant difference in the mean age at initial presentation between the three groups, all further analysis for various parameters was analyzed adjusting for age. Serum calcium was significantly lower in protocol 1 compared to protocols 2 ( $p < 0.001$ ) and 3 ( $p < 0.001$ ) at 8 weeks and 20 weeks after adjusting for age. There was no statistically significant difference in serum calcium between protocols 2 and 3 either at baseline or at 8 and 20 weeks. Serum phosphorous was significantly lower in protocol 1 compared to 2 at baseline ( $p = 0.002$ ), at 8 weeks ( $p = 0.008$ ) and at 20 weeks ( $p = 0.03$ ); between protocols 1 and 3 at baseline ( $p = 0.004$ ), at 8 weeks ( $p = 0.05$ ) at 20 weeks ( $p = 0.01$ ). There was no statistically significant difference in serum phosphorus between protocols 2 and 3 either at baseline, 8 and 20 weeks. The 25 OHD levels were not different between the three protocols at baseline. At 8 weeks and 20 weeks there was a statistically significant increase in 25 OHD levels compared to baseline in all three protocols ( $p < 0.001$ ). At 8 and 20 weeks 25 OHD levels were significantly different between protocols 1 and 2 ( $p = 0.01$  at 8 weeks,  $p = 0.001$  at 20 weeks). Comparison of 25 OHD levels at 8 weeks and 20 weeks between protocols 1 and 3 showed significant difference ( $p = 0.01$  at 8 weeks and  $p = NS$  at 20 weeks). Comparison of 25 OHD levels at 8 weeks and 20 weeks between protocols 2 and 3 showed significant difference ( $p = 0.001$  at 8 weeks; and  $p = 0.001$  at 20 weeks). Gender did not influence the 25OHD levels in any of the groups. The PTH

**Table 1: Comparison of three protocols of treatment**

Variable	Protocol 1	Protocol 2	Protocol 3
Age (Years)	31.5 ± 6.3	44.6 ± 13.8†	49.5 ± 14.5
Baseline (No.)	41	35	56
Serum creatinine (mg/dL)	0.8 ± 0.1	0.7 ± 0.2	0.8 ± 0.1
Serum albumin (gm/dL)	4.1 ± 0.3	4.3 ± 0.6	4.2 ± 0.43
Serum calcium (mg/dL)	9.1 ± 0.5	9.3 ± 0.5	9.2 ± 0.5
Serum phosphorous (mg/dL)	3.3 ± 0.4	3.7 ± 0.6	3.6 ± 0.4
SAP (IU/L)	87.3 ± 16.7	95.1 ± 54.1	98.8 ± 50.2
Serum 25OHD (ng/mL)	8.6 ± 5.1	8.0 ± 4.2	8.5 ± 5.1
Serum PTH (pg/mL)	57.1 ± 28.4	47.2 ± 19.4	53.5 ± 30.7
8 Weeks (No.)	41	35	56
Serum calcium (mg/dL)	8.8 ± 0.3	9.3 ± 0.5†	9.2 ± 0.5*
Serum phosphorous (mg/dL)	3.5 ± 0.6	3.7 ± 0.4‡	3.6 ± 0.4
SAP (IU/L)	84.1 ± 16.9	83.3 ± 42.5	85.5 ± 41.7
Serum 25 OHD (ng/mL)	44.2 ± 19.9	36.5 ± 13.8§	26.05 ± 14.4*
Serum PTH (pg/mL)	34.4 ± 17.6	34.6 ± 13.1	31.2 ± 12.8
20 Weeks (No.)	41	23	30
Serum creatinine (mg/dL)	0.9 ± 0.2	0.7 ± 0.1	0.8 ± 0.1
Serum albumin (gm/dL)	4.3 ± 0.7	4.2 ± 0.3	4.2 ± 0.4
Serum calcium (mg/dL)	8.7 ± 10.0	9.6 ± 0.5†	9.3 ± 0.6†
Serum phosphorous (mg/dL)	3.4 ± 0.5	3.6 ± 0.4	3.6 ± 0.5
SAP (IU/L)	84.4 ± 19.0	80.0 ± 40.6	84.5 ± 39.3
Serum 25OHD (ng/mL)	34.8 ± 18.2	58.2 ± 22.9†	33.0 ± 16.0§
Serum PTH (pg/mL)	35.2 ± 23.2	36.8 ± 20.3	30.9 ± 10.0

Data are expressed as mean ± standard deviation. See text for details regarding the treatment protocols

\* protocol 1 vs protocol 3, p<0.001

† protocol 1 vs protocol 2, p<0.001

‡ protocol 1 vs protocol 2, p =0.02

§ protocol 2 vs protocol 3, p<0.001

SAP = serum alkaline phosphatase; 25 OHD = 25-hydroxy vitamin D; PTH = parathyroid hormone

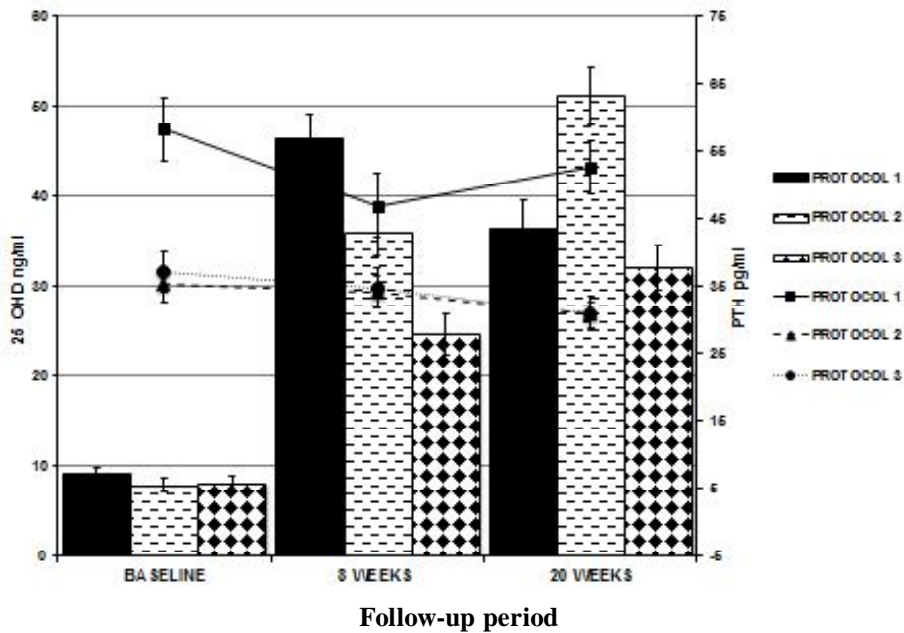
levels were not different between the protocols at base line, 8 and 20 weeks (Figure 1).

The proportion of subjects with 25OHD deficiency, insufficiency and sufficiency receiving the three protocols at baseline, 8 weeks and 20 weeks is shown in Figure 2.

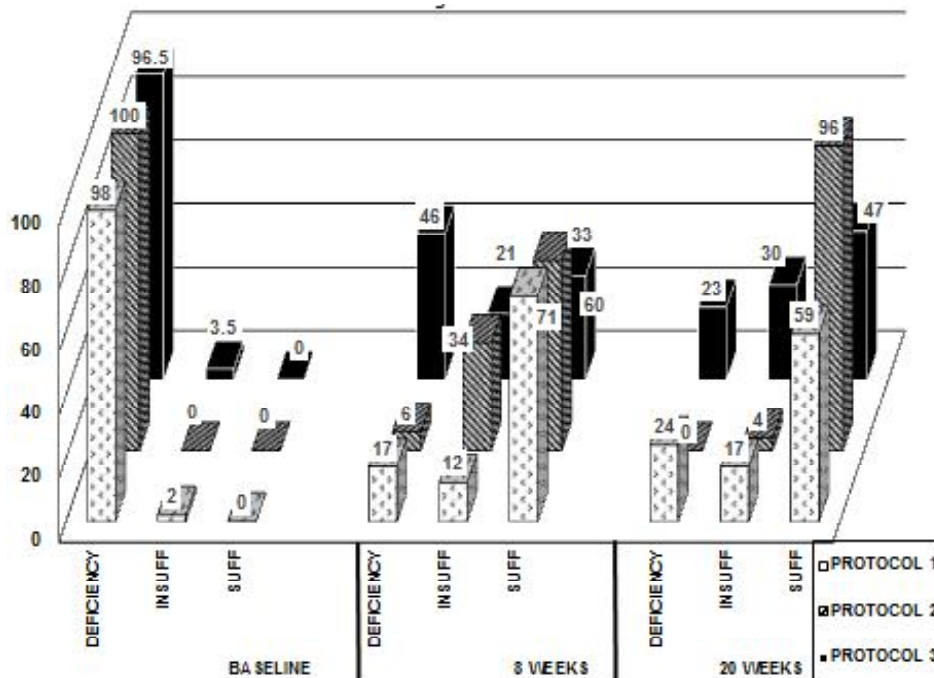
## DISCUSSION

Achieving and maintaining therapeutic vitamin D sufficiency levels, has certainly proved challenging. There were previous studies<sup>20-23</sup> from the Indian sub-continent looking at different strategies of vitamin D replacement

in deficient subjects using varying doses of vitamin D with or without calcium for variable lengths of time.<sup>20-23</sup> A study from New Delhi<sup>20</sup> confirmed that a dose of 60,000 IU of cholecalciferol (1500 µg) per week in addition to 500 IU (12.5 µg) administered daily along with elemental calcium resulted in improving vitamin D to sufficiency levels in most subjects and suppressed previously elevated PTH to within normal range at 8 weeks. Similar results were reported in another study.<sup>16</sup> But, neither rise in vitamin D levels nor PTH suppression was sustained at the end of one year. Similarly,



**Figure 1:** Serum 25 OHD (bars) and PTH (lines) levels at baseline and during follow-up  
 25 OHD = 25-hydroxy vitamin D; PTH = parathyroid hormone



**Figure 2:** Proportion of subjects with vitamin D insufficiency, deficiency and sufficiency at the baseline and while on treatment with three protocols at various time points  
 INSUFF = insufficiency; SUFF = sufficiency

an earlier study<sup>22</sup> looked into this issue and concluded that using 30 ng/dL as the cut-off for vitamin D sufficiency, only 23% of subjects achieved vitamin D sufficiency in 2 months after loading dose (9572 IU/day + 1 g of elemental calcium/day for 2 months) and this improved to 46% at the end of 5 months (3 months of supplemental doses of 3000 IU/day + 1 g of elemental calcium). Subjects dropped their PTH levels by 38% at 2 months but maintained that suppression at 5 months.<sup>22</sup> A randomized study<sup>23</sup> suggested that even cholecalciferol administered in a dosage of 1000 IU daily for 3 months was found inadequate to attain vitamin D sufficiency. The reason behind this failure to active vitamin D sufficiency levels after initial supplementation with high doses was not explored previously.

Efficacy and safety of annual intramuscular injection of a mega dose of cholecalciferol (600,000 IU) was evaluated in a study.<sup>10</sup> Compared with base line [ $32 \pm 8$  nmol/L ( $12.8 \pm 3.2$  ng/mL)] serum 25OHD levels were significantly higher at 4 months [ $114 \pm 35$  nmol/L ( $45.6 \pm 14$  ng/mL)], and 12 months [ $73 \pm 13$  nmol/L ( $29.2 \pm 5.2$  ng/mL)] ( $p < 0.001$ ), increasing by an average of 128% over the 12 months. Compared with base line a corresponding decrease in serum PTH levels was observed was observed at 4 months and at 12 months, with a 30% decrease over 12 months from baseline ( $p < 0.01$ ). In a similar study<sup>24</sup> patients with vitamin D insufficiency ( $<30$  ng/mL) were randomized to receive either intramuscular (IM) ( $n = 34$ ) or oral ( $n = 32$ ) cholecalciferol. Each group received one dose of 600,000 IU cholecalciferol. Cholecalciferol was given by intragluteal injection (2 ampoules of Devit3® 300,000 IU, each ampoule containing 1 mL) in IM group. A clinical nurse prepared the oral treatment pouring it on a piece of bread and observed the patients until they consumed the entire piece of bread. Following this compared with baseline ( $11.8 \pm 7.6$  ng/mL) mean serum 25 OHD levels increased

significantly at 6<sup>th</sup> week ( $32.7 \pm 9$  ng/mL) and at 12<sup>th</sup> week ( $52.3 \pm 14.2$  ng/mL) in IM group ( $p < 0.0001$ ). Corresponding levels in oral group were  $47.6 \pm 12.7$  ng/mL,  $42.9 \pm 13.4$  ng/mL and  $14.9 \pm 6.9$  ng/mL, respectively ( $p < 0.0001$ ). Increase serum 25 OHD level in IM group was significantly higher than oral group ( $p = 0.003$ ) at 12<sup>th</sup> week. In both groups PTH levels decreased significantly at 6<sup>th</sup> and 12<sup>th</sup> weeks compared to baseline ( $p = 0.0001$ ) with no difference between these two groups themselves.

A systematic review<sup>25</sup> looking at the effectiveness of single large dose of vitamin concluded that doses above 300,000 IU given once were successful in achieving vitamin D levels within one week and was also shown to be successful in maintaining long term (1 year) suppression of PTH.

In this study, we compared the efficacy of parenteral Vs oral therapy in achieving desired vitamin D status and also compared to see if intensive therapy (by regular reminders/supervision) would be superior to routine therapy. To date we are not aware of any such study done so far in our country. In our study population, although proportion of patients in intensive oral therapy achieved better 25 OHD levels at 2 months compared to standard oral therapy ( $44.2 \pm 19.9$  Vs  $26.1 \pm 14.4$  ng/mL), these differences were not sustained at 5 months ( $34.8 \pm 18.2$  Vs  $33.0 \pm 16$  ng/mL) underlining the importance of continued supervision. Proportion of patients with sufficient 25OHD levels were statistically non-significant between the two kinds of oral therapy at 5 months. Unlike these two groups, proportion of study population that achieved sufficient vitamin D levels ( $58.2 \pm 23$  ng/mL) were significantly higher with the parenteral therapy at 5 months. Despite this failure to sustain vitamin D levels, PTH level dropped significantly in all three groups within the first two months of therapy

and was sustained throughout ( $57.1 \pm 28.4$  to  $35.17 \pm 23.3$  Vs  $53.5 \pm 30.7$  to  $30.9 \pm 9.9$  pmol/L in intensive and standard oral regimens and  $47.2 \pm 19.4$  Vs  $36.8 \pm 20.4$  pmol/L in parenteral therapy).

These results support parenteral therapy as a superior therapeutic strategy over oral therapy in achieving sustained levels of vitamin D levels in longer term. This study also shows that intensive oral vitamin D supplementation in the form of support and supervision is only effective as long as the effort is sustained and loses its efficacy soon after (3 months in our study). Our study results show that ongoing supplementation with vitamin D is necessary to sustain the effect and failure of therapy is likely to be due to poor compliance. Parenteral therapy hence remains an effective alternative.

These results assume greater significance when developing strategies to improve vitamin D status of population at large via supplementation. We are aware that this is a study with a small sample size and this study needs to be replicated in a larger sample before coming to definitive conclusions. Nevertheless, this study shows that loading doses of vitamin D in parenteral form followed by routine oral replacement proved more effective in sustaining higher vitamin D levels than oral therapy alone and supervised intensive oral loading doses appears better than routine loading doses in achieving vitamin D adequacy proving the role of good compliance.

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