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Research Article

EFFECT OF SINGLE INJECTION OF VITAMIN D (CHOLECALCIFEROL, 6 LAC IU) IN ADULTS: DOES BODY MASS INDEX DETERMINE DOSAGE FREQUENCY AND RISE IN SERUM 25(OH)D_3 LEVEL?

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ABSTRACT

Objective: Vitamin D deficiency (VDD) is a widespread problem in all age groups and socioeconomic strata. Cholecalciferol intramuscular (IM) injections are often prescribed to treat VDD. Response to cholecalciferol injection is not uniform in all subjects.

Methods: We enrolled 65 ostensibly healthy adult volunteers in a vitamin D awareness camp. They were screened for VDD by measuring their serum 25(OH)D_3 level. Of 65 subjects, 58 were found to be deficient, 2 insufficient and 5 sufficient. Their body mass indices (BMI) were calculated by measuring height and weight. A total of 31 subjects preferred taking single IM injection of cholecalciferol (6 lac IU) to correct their deficiency and decided to comply with follow-up 25(OH)D_3 measurement at day 15, 60 (2 months) and 180 (6 months).

Results: Mean values for 25(OH)D_3 in 31 subjects were 12.88±2.55 ng/ml, 29.33±14.40 ng/ml, 47.27±11.09 ng/ml, and 24.59±8.19 ng/ml at baseline, day 15, 60, and 180. Mean 25(OH)D_3 levels at baseline, day 15, 60, and 180 were 12.80±2.40 ng/ml, 24.85±10.60 ng/ml, 44.76±8.85 ng/ml, and 25.05±9.62 in "obese" subjects, 13.50±3.06 ng/ml, 28.25±11.45 ng/ml, 44.70±10.40 ng/ml, and 24.48±6.81 in "overweight" individuals and 12.43±2.72 ng/ml, 44.06±19.26 ng/ml, 61.16±6.96 ng/ml, and 23.33±5.42 in "normal" subjects. Values between groups were found to be significantly different at day 15 and 60 after applying one-way ANOVA.

Conclusion: All subjects, after taking single cholecalciferol IM injection (6 lac IU), had their 25(OH)D_3 levels raised to normal within 2 months but reached insufficient range in 6 months. Though the rise in 25(OH)D_3 was significantly faster in those having normal BMI than in the subjects having higher BMI. One injection of 6 lac IU cholecalciferol, every 6 months seems to be an effective and safe way of treating VDD.

Keywords: Vitamin D, Cholecalciferol injection, Body Mass Index, BMI, 25(OH)D_3

INTRODUCTION

Vitamin D, a fat-soluble secosteroid is technically a hormone as its active form 1,25-dihydroxycholecalciferol (1,25$(OH)_2$D) mediates its biological effects by binding to the vitamin D receptor, which is principally located in the nuclei of target cells [1]. Major circulating and storage form of vitamin D is 25-hydroxycholecalciferol (calcifediol, 25(OH)D_3) which is formed in the liver after 25-hydroxylation. It's also the form of vitamin D that's measured in blood tests to detect deficiency of vitamin D. Vitamin D_3 (cholecalciferol) is an important part of calcium homeostasis and it is crucial for bone and muscle development, and for preventing osteoporosis [2]. Osteoporotic patients receiving antiresorptives (bisphosphonate) and anabolic (teriparatide) treatment must have optimal vitamin D status to maximize benefits [3,4].

Vitamin D deficiency (VDD) is a worldwide problem, which may be caused by inadequate intake (poor nutrition, vegetarianism), decreased synthesis in skin (inadequate sunlight exposure, use of sunscreens), loss of ability of kidney to convert cholecalciferol to its active form (calcitriol), obesity (less bioavailability) [5], etc. As per the "Endocrine Society Clinical Practice Guidelines" for evaluation, treatment, and prevention of VDD, VDD has been defined as a 25(OH)D of <20 ng/ml. Vitamin D insufficiency has been defined as a 25(OH)D of 21-29 ng/ml [6,7].

VDD is more prevalent in elderly, women of childbearing age and infants and it often remains unrecognized by clinicians. In a study carried out in Delhi, India, VDD was present in 91.2% of healthy subjects aged >50 years and vitamin D insufficiency in another 6.8% [8].

VDD may not result in any obvious symptoms, but without treatment it can have significant health effects and increase a person's risk of musculoskeletal conditions. VDD in children can cause growth retardation and classic signs and symptoms of rickets. In adults, VDD can precipitate and exacerbate both osteopenia and osteoporosis and increase the risk of fracture [9]. Apart from its clear role in musculoskeletal health, VDD is also associated with increases risk of diabetes mellitus, hypertension, and few autoimmune diseases and cancers [10].

As per the "Endocrine Society Clinical Practice Guidelines," to raise the blood level of 25(OH)D_3 consistently above 30 ng/ml may require at least 1500-2000 IU/day of vitamin D [7]. In the severe deficiency of vitamin D, patients may have to take weekly oral therapy (tablet/soft gelatin capsule/sachet) with 60,000 IU oral vitamin D for at least 8 weeks. Moreover, obese patients may require higher doses as bioavailability of vitamin D is relatively poor in these patients [5].

However, many patients often find daily/weekly oral doses difficult to remember or swallow. Persistence with oral vitamin D supplementation is very low [11]. Compliance to oral therapy is a major limitation in repleting vitamin D levels in the body. Intramuscular (IM) administration of vitamin D may well address this limitation. IM injections of vitamin D are commonly available in two strengths (3 lac and 6 lac IU) in the market.

In VDD/insufficient elderly subjects, IM application has been found to be more effective in increasing 25(OH)D_3 levels and balance performance [12]. Use of vitamin D injections is quite safe if accidental overdose without monitoring serum 25(OH)D_3 levels is not administered.

However, response to cholecalciferol injections and pattern of rise in $25(OH)D_3$ level are not uniform in all subjects which can result in an inaccurate judgment of giving multiple injections in short duration, sometimes even without measuring $25(OH)D_3$ level, by physicians [13]. In one study involving elderly subjects, after administration of one IM injection of vitamin D (6 lac IU), mean serum $25(OH)D_3$ levels increased gradually at 6th week (32.72±9.0 ng/ml), and at 12th week (52.34±14.2 ng/ml) compared with baseline (11.76±7.6 ng/ml) [12] values. In another study involving young subjects, IM injection of 6 lac IU cholecalciferol increased $25(OH)D_3$ level to 77.2±30.5 ng/ml within 3 days from its baseline value of 15.8±6.5 ng/ml [14].

It's a well-established fact that there is an inverse association of serum $25(OH)D_3$ and body mass index (BMI) >30 kg/m^2, and thus, obesity is associated with VDD [5]. However, there are no clear guidelines, evidences, and consensus on the frequency of IM injections needed to replete and/or maintain vitamin D status and pattern of resulting rise in the level of $25(OH)D_3$.

In this current study, we tried to address the above-mentioned lacunae. Subjects having VDD, who preferred taking cholecalciferol injections (IM) to replete their $25(OH)D_3$ levels, were observed and followed up for their subsequent $25(OH)D_3$ measurements and pattern of rise in its level.

METHODS

Totally, 65 apparently healthy adult subjects in a corporate office were enrolled in a vitamin D awareness camp and all were screened for VDD. Their $25(OH)D_3$ levels were measured. Of 65 subjects, 58 were found to be deficient ($25(OH)D_3$ <20 ng/ml), 2 insufficient ($25(OH)D_3$ between 21 and 29 ng/ml), and 5 sufficient (>30 ng/ml). A total of 27 subjects preferred oral regimen of cholecalciferol whereas 31 out of these 58 subjects decided to take single deep IM injection (with less viscous and minimally painful ethyl oleate base) of cholecalciferol (NU-D3®) in gluteal muscle to correct their VDD (day 0). Latter also decided to comply voluntarily with follow-up $25(OH)D_3$ measurements at day 15, 60 (2 months) and 180 (6 months).

BMI of subjects was also calculated by measuring their height and weight. Based on new Indian guidelines for cut-off values of BMI released jointly by the Health Ministry, the Diabetes Foundation of India, the All-India Institute of Medical Sciences, Indian Council of Medical Research and National Institute of Nutrition, subjects were divided into three categories: Obese (BMI >25.0 kg/m^2), overweight (BMI 23.0-24.9 kg/m^2), and normal (BMI 18.0-22.9 kg/m^2) [15]. Baseline values of $25(OH)D_3$ at day '0' were not different significantly between the groups ($p>0.05$). Mean values of $25(OH)D_3$ were compared at day 15, 60 & 180 by using one-way analysis of variance test.

RESULTS

Mean values (±standard deviation) for $25(OH)D_3$ in 31 subjects were 12.88±2.55 ng/ml, 29.33±14.40 ng/ml, 47.27±11.09 ng/ml, and 24.59±8.19 ng/ml at baseline, day 15, 60, and 180, respectively. The subjects, who were having higher BMI, had a slower rise in their $25(OH)D_3$ values after administration of cholecalciferol injection compared to those having low BMI as shown in Table 1 and Fig. 1. No subject reported any local or systemic side effect from the injection. The difference among the groups was found to be statistically significant ($p<0.05$) at day 15 and 60 but not at day 180.

DISCUSSION

Advances in the study of vitamin D and its important role in musculoskeletal health & many other extraskeletal diseases during the past two decades have significantly led to increased awareness among health care professionals, yet VDD is the most under-diagnosed and under-treated nutritional deficiency in the world. Different Indian studies have also reported VDD, as high as 70-100% of apparently healthy individuals [16]. Elderly people also have a high prevalence of VDD[8] with secondary hyperparathyroidism resulting in suboptimal bone health and precipitation or worsening of osteoporosis [17].

The calcium absorptive performance of the gut is a function of a person's $25(OH)D_3$ status [18]. Therefore, before instituting any calcium supplementation or anti-osteoporotic therapy, vitamin D levels must be replenished. About two-thirds of the patients remain non-persistent with oral vitamin D regimen [11]. Compliance with vitamin D supplementation has also been found to be very low in different studies [19,20]. Discontinued vitamin D supplementation has limited the cumulative effect on the gain in bone mass particularly in elderly [21]. Concerning the low compliance attributed to daily pill burden among patients taking concomitant medications for comorbid conditions or forgetfulness among elderly, high dose (6 lac IU) IM injection of vitamin D is a well-tolerated, and effective treatment option [12,22]. Injectable cholecalciferol (6 lac IU) appears to be quite safe [12]. Though rare cases of hypervitaminosis D have been reported, they seem to be solely due to inadvertent use of multiple injections without any documentation of serum VDD [13].

Our study has clearly shown that a single IM injection of cholecalciferol (6 lac IU) raised the serum $25(OH)D_3$ level to normal (>30 ng/ml) in all subjects within 2 months. Subjects having normal BMI had faster response to cholecalciferol injections as reflected by a rapid increase in their serum $25(OH)D_3$ values reaching normal within 15 days. In subjects having higher BMI (overweight/obese), the rise in serum $25(OH)D_3$ levels was slower and took up to 2 months to reach normal.

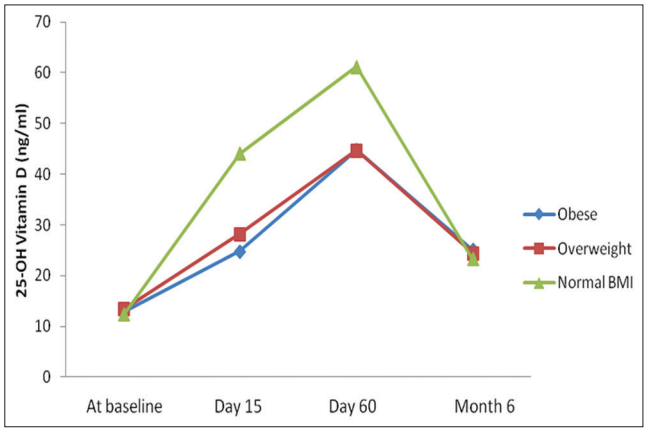

Fig. 1: Change in mean 25(OH)D3 level at day 15, 60 & 180 from baseline in obese, overweight and those having normal BMI

Table 1: Mean values of 25(OH)D3 at baseline (day '0'), day 15, 60 & 180 after administration of single 6 lac IU cholecalciferol IM injection

BMI[#]	Baseline 25(OH) D3	After 15 days	After 60 days	After 180 days
Normal (<23.0) (n=6)	12.43±2.72	44.06±19.26	61.16±6.96	23.33±5.42
Overweight (23.0-24.9) (n=7)	13.50±3.06	28.25±11.45	44.70±10.40	24.48±6.81
Obese (>25.0) (n=18)	12.80±2.40	24.85±10.60	44.76±8.85	25.05±9.62
All (n=31)	12.88±2.55	29.33±14.40	47.27±11.09	24.59±8.19
p-value	0.747	0.013*	0.002*	0.911

[#]As per Indian Guidelines, *Statistically significant. All values in mean±SD (ng/ml). SD: Standard deviation, BMI: Body mass index

Finally, after 180 days (6 months), values of serum $25(OH)D_3$ came down to the insufficient range (21-29 ng/ml) in all subjects suggesting the need of another injection. Based on our study, we can recommend use of one IM injection of cholecalciferol (6 lac IU) every 6 months (twice in a year) to treat VDD and maintain $25(OH)D_3$ level in body irrespective of the BMI of subject/patient.

Our recommendation for use of one injection of cholecalciferol every 6 months is in line with another previous study, where single megadose of cholecalciferol injection (6 lac IU) provided effective therapy for treatment of VDD in adolescents for 3 months but not for 6 months [23].

CONCLUSION

We can infer from this observational study that pattern of rise in $25(OH)D_3$ level is not uniform in all subjects and it depends on BMI, but normal level is attained in all subjects within 2 months. The level of $25(OH)D_3$ invariably reaches insufficient range within 6 months of administering single IM injection of 6 lac IU cholecalciferol in deficient subjects.

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