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Original Article

Efficacy of Vitamin D3 versus Vitamin D2 in Deficient and Insufficient Patients: An Open-Label, Randomized Controlled Trial

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Abstract

Background: Vitamin D deficiency is very common worldwide but highly prevalent in the Gulf region. The clinical manifestations of Vitamin D deficiency vary depending on the severity and duration of the deficiency. Effective treatment should correct the vitamin D levels and improve other metabolic markers. **Objectives:** We aimed to (1) compare the efficacy of Vitamin D3 and Vitamin D2 in terms of raising serum 25(OH) total Vitamin D levels, (2) evaluate the time of its attainment, and (3) demonstrate the effect of replacement with either preparation on serum markers of bone or calcium metabolism. **Patients and Methods:** We conducted a randomized controlled study involving 250 adults with Vitamin D deficiency or insufficiency, assigned into 1:1 ratio to receive weekly capsules of either 50,000 IU of D2 or 50,000 IU of D3 for up to 12 weeks. Serum total Vitamin D level, calcium, phosphorus, alkaline phosphatase, and parathyroid hormone (PTH) levels were measured at 0, 8, and 12 weeks. Analysis of variance and nonparametric test Kruskal–Wallis were used for the comparison of quantitative values and the Chi-square test for comparison of categorical variables. **Results:** After 8 weeks of treatment, the improvement in Vitamin D level was greater for patients in the D3 group (mean = 18.74, standard error [SE] = 1.08) than that for D2 group (mean = 5.88, SE = 0.65), F (1, 240) = 113.840; $P < 0.0005$. Similarly after 12 weeks, the improvement in Vitamin D levels was greater for those in the D3 group (mean = 20.76, SE = 1.14) than that for the D2 group (mean = 7.93, SE = 0.79), F (1, 224) = 90.78; $P < 0.0005$. At 12 weeks, serum calcium, phosphorus, alkaline phosphatase, and PTH levels were not significantly different between the D3 and D2 treatment groups. **Conclusions:** Vitamin D3 is more efficacious and faster in increasing the level of total Vitamin D than Vitamin D2. However, no significant differences were evident on calcium, phosphorus, alkaline phosphatase, or PTH levels between groups.

Keywords: Deficiency, efficacy, Vitamin D2, Vitamin D3

Introduction

Vitamin D deficiency may be caused by reduced sun exposure, decreased intake of vitamin D-containing food or by its reduced absorption, decreased endogenous synthesis (via decreased 25-hydroxylation in the liver as a result of liver disease or decreased 1-hydroxylation in the kidney due to kidney disease), increased hepatic catabolism, or end-organ resistance to Vitamin D.[1] High-risk group for Vitamin D deficiency includes dark-skinned people, obese people, individuals taking medications that accelerate the metabolism of Vitamin D (such as phenytoin), patients on general medical service, institutionalized individuals, individuals with limited effective sun exposure due to protective clothing or consistent use of sunscreens, and those with malabsorption, including inflammatory bowel disease and celiac disease.

Vitamin D has pleiotropic properties in "off-target" sites and can influence cell proliferation, muscle performance, energy metabolism, and bone strength, independent of its actions on calcium absorption.[1] Vitamin D deficiency leads

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to osteomalacia and rickets. There is a compelling body of evidence demonstrating that severe Vitamin D deficiency is associated with cardiovascular disorders[2-6] and with conditions such as immune deficiency, diabetes mellitus (DM), arterial hypertension, and cancer.[2-6] Twelve-month Vitamin D supplementation of treatment-naïve patients with Type 2 DM resulted in the improvement of several cardiometabolic parameters.[7]

The clinical manifestations of Vitamin D deficiency depend on the severity and duration of the deficiency. The majority of patients with mild-to-moderate Vitamin D deficiency are asymptomatic, whereas severe Vitamin D deficiency causes secondary hyperparathyroidism with phosphaturia, osteoporosis, increased risk of fracture, demineralization of bones and, when prolonged, to osteomalacia and rickets in adults and children, respectively.[8] Associated symptoms may then include bone pain and tenderness, muscle weakness, fracture, and difficulty in walking. The prevalence of Vitamin D deficiency is reported to be around 81% in the Middle East. In women, it may be affecting two-thirds, and studies of measurements made in one UAE secondary care institution reached over 96%.[9]

Vitamin D exists in two main forms namely cholecalciferol (Vitamin D3) and ergocalciferol (Vitamin D2). These are both pro-hormones and vitamins. Vitamin D2 is obtained mainly by irradiation of plants or supplemented foods and is found in dairy-free milk, whereas Vitamin D3 is formed in the skin after exposure to sunlight.[10] The 24-hydroxylation step demarcates the impact of ergocalciferol compared with that of cholecalciferol.[11] Several studies evaluated the efficacy of various formulations, dose regimens, and routes of administration of Vitamin D. Vitamin D3 has an increased potency of up to ten folds over Vitamin D2, as the levels of 25(OH) Vitamin D increase more significantly and are maintained to a higher level for a longer time with Vitamin D3 than with Vitamin D2.[12-16] A handful of studies were done in the MENA region to confirm these results in its population where Vitamin D deficiency is reaching epidemic order on magnitude; establishing the most effective replacement strategy is of paramount importance. Hence, the aim of this study is to compare the efficacy of Vitamin D2 versus Vitamin D3 in increasing total serum Vitamin D level in our local population.

Patients and Methods

Design

The study was an open-label, prospective, randomized study of adult patients with Vitamin D deficiency or insufficiency. Patients were randomly allocated to two groups, in which 125 patients were given one capsule of 50,000 IU Vitamin D2 per week for up to 12 weeks and their 25(OH) Vitamin D total (D2 + D3) was checked at 0, 8, and 12 weeks. The remaining 125 patients were given 50,000 IU Vitamin D3 per week for up to 12 weeks and their 25(OH) Vitamin D total (D2 + D3) was checked at 0, 8, and 12 weeks. Patients' adherence to these regimens was confirmed through giving each patient a telephone call; during this call, they were also reminded about their following appointment for measuring Vitamin D, calcium, phosphate, and parathyroid hormone (PTH) levels.

Treated patients of either group whose 25(OH) Vitamin D total level reached the normal sufficient value of 30 ng/ml or above at 8 weeks were terminated. Calcium, phosphorus, alkaline phosphatase, and PTH levels of all the study patients were available (sixty patients in Vitamin D2 group and sixty patients in Vitamin D3 group) at 0, 8, and 12 weeks with 25(OH) Vitamin D total [Table 1]. No further testing was done for calcium, phosphorus, alkaline phosphatase, and PTH levels of patients of either group whose 25(OH) Vitamin D total level reached the normal range at or above 8 weeks of treatment .

The study population included UAE national patients, admitted in the internal medicine department of Rashid hospital and those local patients of both genders visiting the outpatient medical clinic, and nonlocal patients, of both genders, visiting the medical staff clinic, who were found to have Vitamin D deficiency or insufficiency. Patients who have been on any type of Vitamin D supplement; patients on drugs which affect the levels of Vitamin D such as phenytoin, phenobarbital, prednisolone (affect metabolism), orlistat, and cholestyramine (affect absorption); patients with estimated glomerular filtration rate <30 ml/min; and patients in stages IV and V chronic kidney disease were all excluded from the study.

Medications

Soft gel capsules containing 10,000 U of Vitamin D3 were purchased from Nature's Bounty company (Ronkonkoma,

Table 1: Baselines characteristics and some measurements of mineral metabolism at 0, 8, and 12 weeks

Parameters	D_2 (n=156)	D_3 (n=123)
Age (years), mean±SD	51.4±17	47.1±16.6
Gender (%)		
Female	81 (52)	64 (52)
Male	75 (48)	59 (48)
Baseline serum Vitamin D level	13.8±6.2	14.8±6.2
Ethnicity (%)		
UAE	126	99
Non-UAE Arabs	11	10
Asians	20	14
Serum calcium (weeks)		
0	9.23±0.51	9.38±0.43
8	9.14±0.42	9.41±0.50
12	9.12±0.38	9.31±0.65
Serum phosphorus (weeks)		
0	3.42±0.58	3.52±0.57
8	3.47±0.47	3.56±0.45
12	3.53±0.57	3.74±0.48
Serum alkaline phosphatase (weeks)		
0	78.4±26.6	79.1±30.4
8	78.3±26.2	77.9±23.5
12	78.3±23.4	79.3±18.7

SD: Standard deviation

NY, USA), and Vitamin D2 capsules, which were also soft gels containing 50,000 U, were purchased from Europharm company, Saint-Léonard, Canada; each of the above products expires 3 years from the manufacturing date.

Biochemical measurements

Electrochemiluminescence analyzer was used to measure Vitamin D. This assay does quantitative determination of total 25(OH) Vitamin D in serum plasma. This assay does quantitative determination of total 25(OH) Vitamin D in serum plasma via a Vitamin D-binding protein which capture protein to bind Vitamin D3 and Vitamin D2. Results were determined through calibration curve, which is an instrument specifically generated by two-point calibration and master curve provided by reagent bar code. The intra-assay coefficient of variations (CVs) were done on two levels: level 1: 0.03 (3.36%) and level 2: 0.02 (2.17%), whereas the interassay CVs were as follows: level 1: 0.02 (2.45%) and level 2: 0.01 (1.27%). The serum 25(OH) D concentrations <10 were considered to indicate Vitamin D deficiency according to our lab references, while concentration between 10 and 29.9 was considered to indicate Vitamin D insufficiency. The serum intact PTH was measured by using the radioimmunoassay technique on the Gamma counter WIZARD 1470 (Perkin Elmer Wallac, Waltham, Massachusetts, U.S). Serum calcium levels were measured by NM-BAPTA method, whereas the serum phosphate levels were measured by molybdate ultraviolet.

Statistical analysis

Data were processed using the SPSS software, SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA) and expressed as mean and standard deviation. We used analysis of variance and nonparametric tests such as Kruskal–Wallis for the comparison of quantitative values and the Chi-square test for categorical variables.

Results

After 8 weeks of treatment, the improvement in Vitamin D level was greater for patients in the D3 group (mean = 18.74, standard error [SE] = 1.08) than that for D2 group (mean = 5.88, SE = 0.65), $F(1, 240) = 113.840$; $P < 0.0005$. Similarly after 12 weeks of treatment, the improvement in Vitamin D levels was greater for those in D3 group (mean = 20.76, SE = 1.14) than that for D2 group (mean = 7.93, SE = 0.79), $F(1, 224) = 90.78$; $P < 0.0005$ [Figure 1].

After 12 weeks, there was no significant difference in the calcium levels between the D3 group (mean = 0.013, SE = 0.099) and D2 group (mean = 0.036, SE = 0.0695), $F(1, 68) = 0.026$; $P = 0.873$, or phosphorus levels between the D3 (mean = 0.207, SE = 0.1435) and the D2 groups (mean = 0.078, SE = 0.076), $F(1, 66) = 0.606$; $P = 0.439$, or in the parathyroid levels between the D3 (mean = 1.91, SE = 2.38) and the D2 groups (mean = 0.61, SE = 1.01), $F(1, 66) = 0.315$; $P = 0.576$, or in the alkaline phosphate levels between the D2 (mean = −0.111, SE = 2.21) and the D3 groups (mean = 2.86, SE = 2.32), $F(1, 66) = 0.433$; $P = 0.513$ [Tables 2 and 3].

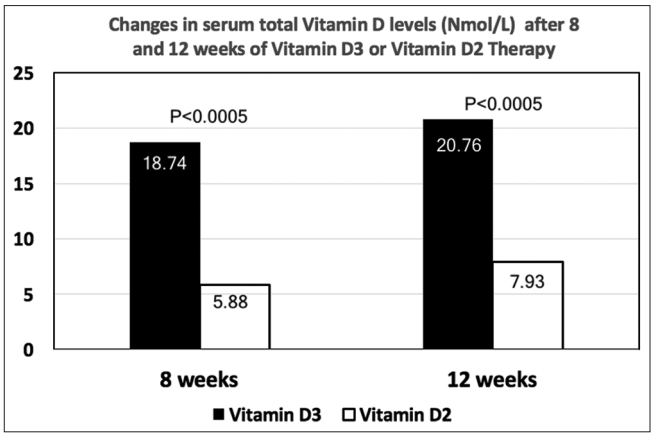

Figure 1: Changes in Vitamin D levels after 8 and 12 weeks of Vitamin D3 or Vitamin D2 therapy

Table 2: Changes in serum calcium, phosphorus, alkaline phosphatase, and intact parathyroid hormone after 12 weeks

Groups	Vitamin D3 group	Vitamin D2 group
Serum calcium	0.013±0.099	0.036±0.0695
	$F(1, 68)=0.026$; $P=0.873$	
Serum phosphorus	0.207±0.1435	0.078±0.076
	$F(1, 66)=0.606$; $P=0.439$	
Serum alkaline phosphate	−0.111±2.21	2.86±2.32
	$F(1, 66)=0.433$; $P=0.513$	
Serum intact PTH level	1.91±2.38	0.61±1.01
	$F(1, 66)=0.315$; $P=0.576$	

Values are shown as mean±SEM. PTH: Parathyroid hormone, SEM: Standard error of mean

Among the total 50 inpatients, 35 were on Vitamin D2 and 15 were on Vitamin D3. Among the 230 outpatients, 120 were on Vitamin D2 and 110 were on Vitamin D3. Eleven patients dropped out from the inpatient group (six were on D2 and five were on D3). Twenty-seven patients dropped out from the outpatient group (13 were on D3 and 14 were on D2).

Discussion

The present study evaluated the Vitamin D levels and associated variables in response to Vitamin D3 versus Vitamin D2 over 8–12 weeks in a population known to have a high prevalence of Vitamin D deficiency and insufficiency. Vitamin D3 has an increased potency of up to 10 folds over Vitamin D2, as the levels of 25(OH) Vitamin D increase more significantly and are maintained to a higher level for a longer time with Vitamin D3 than with Vitamin D2. It has been shown that, over a time course, cholecalciferol induces a quicker response in the production of serum 25(OH) D that sustains longer at higher concentrations than ergocalciferol.[12,13] Armas *et al*.[12]

Table 3: Improvement in biochemical variables over time in patients with Vitamin D deficiency and insufficiency according to treatment

Parameters	Time point		*P*
	0 week versus 8 weeks	0 week versus 12 weeks	
Patients pretreatment (*n*)			
Vitamin D2/Vitamin D3	136/106	129/97	
Serum 25(OH)D (ng/ml)			
Vitamin D2	5.8801±7.61794	7.9279±8.98217	*P*<0.0005
Vitamin D3	18.7396±11.09842	20.7557±11.25213	
Serum calcium (mg/dl)			
Vitamin D2	0.038±0.4464	0.036±0.5151	*P*=0.219 (0-8 weeks); *P*=0.873 (0-12 weeks)
Vitamin D3	0.058±0.3928	0.013±0.3833	
Serum PTH (mg/dl)			
Vitamin D2	−0.266±7.7348	0.607±7.3964	*P*=0.55 (0-8 weeks); *P*=0.439 (0-12 weeks)
Vitamin D3	1.948±6.3207	1.907±8.9054	
Serum phosphate (mg/dl)			
Vitamin D2	0.056±0.4579	0.078±0.5582	*P*=0.55 (0-8 weeks); *P*=0.439 (0-12 weeks)
Vitamin D3	0.004±0.4875	0.207±0.5370	
Alkaline phosphatase (unit/L)			
Vitamin D2	−1.029±15.7233	−0.111±16.2303	*P*=0.096 (0-8 weeks); *P*=0.576 (0-12 weeks)
Vitamin D3	−2.192±12.9085	2.857±8.6989	

Changes are expressed as mean±SD. PTH: Parathyroid hormone, SD: Standard deviation, 25(OH) D: 25-hydroxyvitamin D

used a single bolus of 50,000 IU that was given to thirty patients between the ages of 20 and 61 years. The initial rise in 25(OH) Vitamin D levels in the first 3 days was similar, with both the types of vitamins indicating similar absorption with both, but serum 25(OH) D2 concentrations fell rapidly back to baseline after only 14 days, whereas serum 25(OH) D3 concentrations peaked over this time and had not returned to baseline at the end of the 28-day period, displaying a greater 28-day area under the curve (AUC) for cholecalciferol than for ergocalciferol. The decline in 25(OH) Vitamin D levels with Vitamin D2 that occurred after the 3rd day is most reasonably explained by the quicker metabolism or the rapid clearance of the Vitamin D2 metabolite. Weekly doses of 50,000 IU (for 12 weeks) induced AUC values for cholecalciferol that were significantly greater than those for ergocalciferol. It was also noted that, once Vitamin D is stopped at week 12, there is far greater degradation of 25(OH) D2 (ergocalciferol) than 25(OH) D3 (cholecalciferol).[13] In another study, a daily dose of 1600 IU, of Vitamin D2 or D3, was compared with once-monthly (50,000 IU) dose of each of these vitamins over a 12-month period in Australia.[14] Vitamin D3 was shown to be significantly more effective than Vitamin D2 at raising serum 25(OH) D concentration for the daily dosage ($P = 0.05$) and for daily and monthly dosage groups combined.[14] Romagnoli *et al*. compared single oral and intramuscular doses of 30,000 IU of Vitamin D2 and Vitamin D3 in Pakistan.[15] Vitamin D3 was significantly more potent at increasing serum 25(OH)D concentrations than Vitamin D2 for both the oral and intramuscular routes.[15] Furthermore, Lehmann *et al*.[16] compared the bioavailability of Vitamin D2 and Vitamin D3 supplementation using 50 mcg/day doses of Vitamin D2 or Vitamin D3 or a placebo, over a period of 8 weeks, in healthy volunteers in the USA. They showed that Vitamin D3 increases the total 25(OH) D concentration more than Vitamin D2. Vitamin D2 supplementation was associated with a decrease in 25(OH)D3, which can explain the different effect on total 25(OH)D.[16]

25(OH) Vitamin D total (25[OH]D2, 25[OH]D3) is the best measure of the stores and status of Vitamin D. It is the main circulating form of Vitamin D, and it has a half-life of 15 days, whereas 1,25 Vitamin D circulates in much lower concentrations; has a much shorter half-life of about 4–15 h; and fluctuates with changes in calcium, PTH, and kidney function.

Our study has shown that Vitamin D3 is more potent and faster in increasing the level of 25(OH) Vitamin D as compared to Vitamin D2. We noticed that the level of 25(OH) Vitamin D increased significantly in 8 weeks with Vitamin D3 as compared to Vitamin D2. However, the effect on calcium, phosphate, alkaline phosphatase, and PTH levels was not significant when the level of 25(OH) Vitamin D was increased.

The limitation of our study was that the follow-up of the Vitamin D levels for these patients was not done beyond 12 weeks; therefore, there were only few patients who achieved Vitamin D levels in the higher end of the reference range, and that is why it could not be analyzed if higher levels of Vitamin D had significant effect on calcium, phosphorus, and PTH levels. Furthermore, we did not study the symptomatic improvement in our patients following the replenishment of Vitamin D; however, these may be soft end points to document precisely. Further studies need to be done in this context provided they employ the appropriate tools for symptomatic assessments. Another limitation was that the treatment was

stopped after 8 weeks for those patients whose Vitamin D level reached the normal value.

Conclusions

This study showed that Vitamin D3 is more potent and faster in increasing the level of 25(OH) Vitamin D3 compared to Vitamin D2, as we noticed that the level of 25(OH) Vitamin D increased significantly in 8 weeks with Vitamin D3 as compared to Vitamin D2. However, the effect on calcium, phosphate, alkaline phosphatase, and PTH levels was not significant. Long-term studies are needed to ascertain any meaningful long-term differences in the benefits on bone health and other variables between these two Vitamin D formulations in our population to support favoring one over the other.

Authors' contributions

All authors contributed to the study conception, its planning, data collection and analysis. They have developed their assigned parts of the manuscript and reviewed the other parts. All authors reviewed and agreed the final version of the manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

The study was approved by the Research Ethical Committee of Dubai Health authority, Dubai, UAE and all participants provided informed consent.

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