original article

Effects of a 10-day course of a high dose calciferol versus a single mega dose of ergocalciferol in correcting vitamin D deficiency

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BACKGROUND AND OBJECTIVES: The correction of vitamin D deficiency is crucial for optimal skeletal and non-skeletal health. Most regimens in current use are based on daily dosing, which may raise concerns of dosage inadequacy and suboptimal patient compliance. Vitamin D is available in 2 forms: D2 (ergocalciferol) and D3 (cholecalciferol). It has been reported that D2 supplements are less effective and may enhance the degradation of 25-hydroxyvitamin D3 (25[OH]D3) metabolite. The aim of this study was to compare the effect of 2 high-dose oral vitamin D regimens—a 10-day course of D3 500 000 IU versus a single mega dose of 600 000 IU D2—on serum 25(OH)D levels.

DESIGN AND SETTINGS: A prospective cohort study was conducted from September 2010 to February 2011 in an urban university tertiary hospital in Amman, Jordan.

PATIENTS AND METHODS: A total of 109 patients aged 18 to 79 years were enrolled with severe vitamin D deficiency. Fifty-one subjects received 600 000 IU D2 orally and 54 subjects received a total dose of 500 000 IU D3 administered orally, as 50 000 IU D3 daily for 10 consecutive days. Baseline and follow-up total serum 25(OH)D, 25(OH)D2, and 25(OH)D3 levels were compared.

RESULTS: The mean total 25(OH)D increment from baseline was 10.33 (5.68) ng/mL over a mean of 43.08 (2.81) days for the D2 group. The mean increment in 25(OH)D for the D3 group was 47.03 (23.67) ng/mL over a mean of 36.9 (2.9) days. The difference between the 2 mean increments was highly significant: $P=3.15\times10^{-18}$. The 600 000 IU D2 single mega-dose decreased 25(OH)D3 levels by an average of 4 ng/mL in 37 subjects.

CONCLUSION: Overall, the 10-day oral D3 regimen rapidly and effectively normalized 25(OH)D levels. The shortened dosing interval over 10 consecutive days might result in higher compliance.

The increased awareness of vitamin D deficiency and its consequences on optimal health requires an appropriate evaluation of vitamin D repletion regimens for deficient patients. Vitamin D deficiency leads to secondary hyperparathyroidism, increased bone turnover and bone loss, predisposing individuals to osteoporosis and osteoporotic fractures.[1,2] In addition, it is associated with a variety of chronic diseases such as certain cancers, cardiovascular diseases, autoimmune diseases, muscle weakness and chronic pain, diabetes (types 1 and 2), schizophrenia, and depression.[3-12] Despite ongoing controversy, many experts agree that vitamin D deficiency is defined as circulating levels of 25-hydroxyvitamin D (25[OH]D) less than 20 ng/mL.[8,13] For the correction of vitamin D deficiency, many treatment modalities that are heterogeneous with respect to dose, dosing interval, and formulation of vitamin D supplementation are available.[3,14-16] Although humans produce vitamin D3 (cholecalciferol) endogenously, vitamin D supplements exist in 2 distinct forms. Vitamin D2 (ergocalciferol) is manufactured from irradiation of ergosterol from yeast.

Vitamin D3 is manufactured by irradiating 7-dehydrocholesterol obtained from the lanolin in sheep's wool with ultraviolet B radiation.[8] Despite both forms being used interchangeably for vitamin D repletion, there have been conflicting data published about the equipotency of vitamins D2 and D3; there is also a concern that vitamin D2 might increase catabolism of 25(OH)D3.[17-19] Several studies comparing the 2 forms in a head-to-head manner suggest that they are equally effective in raising total serum 25(OH)D,[20-24] while others suggest that vitamin D2 is less effective.[18,19] These comparative studies used doses of both vitamins D2 and D3, ranging from 1000 to 50 000 IU. Serum 25(OH)D levels following oral vitamin D supplementation permit larger dosing. In addition, there is a concern that vitamin D supplementation doses are frequently inadequate and that adherence with daily medication is likely to be suboptimal. Therefore, less frequent administration may be a practical alternative to daily supplementation.[25]

The present study sought to compare 25(OH)D responses with 2 high-dose vitamin D2 and vitamin D3 regimens, and to observe the change in serum 25(OH)D3 levels following the supplementation of an ergocalciferol mega-dose.

PATIENTS AND METHODS

The subjects were 89 women and 16 men aged between 18 and 79 years, in good general health, who attended Jordan University Hospital (JUH) outpatient clinics (orthopedics, rheumatology, endocrinology, surgery, and family medicine) between September 2010 and February 2011. Exclusion criteria included a serum 25(OH)D level >20 ng/mL, creatinine clearance <20 mL/min, pregnancy and lactation, presence of hepatic disease, malabsorption states and granulomatous conditions, history of nephrolithiasis, current glucocorticoid use >6 months, treatment with oral vitamin D supplementation >400 IU/d, and disorders that might influence vitamin D or parathyroid hormone (PTH) metabolism. Patients who were prescribed medications that may interfere with vitamin D metabolism, including anticonvulsants, verapamil, statins, thiazide diuretics, orlistat, and estrogen-containing medications, were also excluded. The inclusion criterion was a baseline serum 25(OH)D <20 ng/mL. Of the 131 eligible participants, 109 agreed to participate in the study. Four of those who agreed to participate were excluded. Two subjects were found to be non-compliant with the regimen, reporting that they took less than 100% of vitamin D3 that was prescribed. Another subject reported that he was taking vitamin D supplements on a weekly basis, and 1 subject disclosed that he was taking oral prednisone.

Sample size

Sample was not statistically calculated because of the following:

(a) There was no available mean value for 25-OH D (vitamin D level) in the Jordanian population. This mean value and its standard deviation are essential for calculating any sample size needed to assess the vitamin D level. Furthermore, this research is a clinical study to assess the mean change in the status of vitamin D deficiency after receiving 2 different high-dose vitamin D regimens (vitamin D2 vs vitamin D3).

(b) Subjects were recruited from those coming to general laboratory at JUH for vitamin D assessment as referred from rheumatology, diabetes, family medicine, and orthopedics outpatient clinics.

(c) Time frame for the study was 90 days (recruitment phase). During this period, any result <20 ng/mL was considered "vitamin D deficient" (n=158); those who met the eligibility criteria (n=131) were invited to participate in the study. A total of 109 subjects consented and 105 completed the study. Thus, the final sample size was 105 subjects.

Randomization Method

(a) Systematic randomized method was used to place every nth subject into the 2 treatment arms (vitamin D2 vs vitamin D3). (Every nth=every second person).

(b) A list of subjects was prepared and numbered from 1 to 109.

(c) The starting point for the placement of subjects was chosen blindly by placing a finger on the list of numbered subjects. This location represented the starting point. In the case of this study, it was subject number 47 who was placed in the vitamin D2 group. The following subject, i.e., number 48 was placed in the vitamin D3 group, and so on.

Treatment

Participants were assigned to 1 of the 2 treatment groups using a minimization algorithm to ensure balanced numbers of men and women between groups. One group (vitamin D3: Biotech vitamin D3-50 [50 000 IU 100 caps]) took 50 000 IU vitamin D3 per day for 10 consecutive days. The second group (vitamin D2: Sterogyl 15 "A" oral solution 600 000 IU/1.5 mL

[alcohol-based, colorless]) took a 600 000 IU vitamin D2 single bolus dose. The baseline doses were administered by study personnel, resulting in 100% compliance. Compliance with subsequent doses was assessed by tablet counts and participants self- reporting.

Vitamin D deficiency was defined as a serum 25(OH)D level <20 ng/mL. Efficacy for each treatment modality was defined as its ability to raise or maintain 25(OH)D levels above 20 ng/mL during the winter months. Serum 25(OH)D2, 25(OH)D3, and total 25(OH)D levels were determined using the liquid chromatography-mass spectrometry method developed and validated at King Abdullah University Hospital laboratories.[26]

Venous blood samples were collected from each subject between February 28 and May 15, 2011, to test for vitamin D deficiency before administering treatment (vitamin D2 or D3). The samples were protected from light, centrifuged, and stored at −78°C until analysis. Participants were not required to fast for blood collection, which was performed by routine venipuncture. Samples were collected in plain gel tubes to separate serum from red cells and allowed to clot for 30–45 min at room temperature. They were then centrifuged at 1792×g for 5 min, before the serum layer was transferred to glass tubes. All specimens were shipped frozen on dry ice to King Abdullah University Hospital and stored at −78°C until thawed for analysis.

Clinical assessment

Details regarding current medication(s) and diseases, and inclusion-exclusion criteria were acquired from patients' hospital records. Other information about subjects was collected through direct interviews using a non-validated questionnaire. The questionnaire contained questions about age, gender, education, (indoor/outdoor) occupation, and dress style. One post-treatment blood sample was collected from each subject 30 to 45 days post-treatment, as it was the most reasonable prearranged period to meet the patients at the same time while they were visiting their attending physicians. This was the most effective and convenient approach for the patients who come from distant geographic locations as well as for the researchers. This is for time, cost, and logistics constraints.

The analysis of all collected samples was completed in 3 days in May 2011. Compliance with vitamin D3 and vitamin D2 regimens was assessed by participants self-reporting. Compliance with vitamin D3 was defined as taking 100% of the tablets prescribed, and for vitamin D2 as taking the single bolus dose of vitamin D2 as prescribed.

Statistical analysis

Data were statistically analyzed using Microsoft Excel (2007) software. A t test was used to test the difference between 2 means, a chi-square test was used to test the association between categorical variables, and an analysis of variance (ANOVA) test was used for the analysis of variance between several means. Data were reported as mean (standard deviation [SD]). All tests were 2-tailed, and a P value <.05 was considered significant.

RESULTS

A total of 105 participants were enrolled in the study: 51 subjects received 600 000 IU vitamin D2 and 54 subjects received 500 000 IU vitamin D3. The participants were 66.3% female and 33.7% male. The females were divided according to their dress style: Hijab (uncovered face and hands) and Niqab (covering all of their bodies) (80.4%) and Western (4.37%). The mean ages were 45.2 (12.4) and 47.4 (14.9), for vitamin D2 and vitamin D3 groups, respectively. Socio-demographic data of the study participants are illustrated in **Table 1**. There was no significant difference between the mean ages of the 2 groups. The mean age for the vitamin D2 group was 47.35 (14.90), CI [43.28-51.42] and for the vitamin D3 group 45.22 (12.36), CI [41.74–48.7]. The mean total 25(OH)D increment from baseline was 10.33 (5.68) ng/mL over a mean of 43.08 (2.81) days for the vitamin D2 group. In the vitamin D3 group, the mean increment in 25(OH)D was 47.03 (23.67) ng/mL over a mean of 36.9 (2.9) days. The difference between the 2 mean increments was highly significant: $P=3.15\times10^{-18}$. Because the mean change in 25(OH)D level was measured over several days (32–45 days for the vitamin D2 group and 30–40 days for the vitamin D3 group), an ANOVA was applied to evaluate this source of variation. For the vitamin D3 group, the ANOVA for the difference between the means did not show any significant difference between the mean changes in serum 25(OH)D (total post-total pre) observed by duration ($P=.65$ for the vitamin D3 group and $P=.42$ for the vitamin D2 group).

Only 40% (20/51) of subjects treated with vitamin D2 attained a level of ≥20 ng/mL compared with 96.3% (52/54) treated with vitamin D3. In addition, only 8% of subjects treated with 600 000 IU vitamin D2 (4/51) attained an optimal level of 25(OH)D3 ≥30 ng/mL, compared with 92.6% (50/54) treated with 500 000 IU vitamin D3. Of the 51 subjects treated with 600 000 IU vitamin D2, 25(OH)D3 serum levels remained <10 ng/mL in 10% of subjects (5/51); they remained classified as severely deficient, despite receiving treatment. The vitamin D status of subjects after treatment with

Table 1. Socio-demographic data of vitamin D2 and vitamin D3 groups.

	Group1 (D2) N=51	Group 2 (D3) N=54	Stat. test	Sig.
Age (mean [SD])	45.2 (12.4)	47.4 (14.9)	*t* test	*P*=.4
Sex				
Male (no. %)	5 (9.8%)	11 (20.4%)	Chi-square test	*P*=.13
Female (no. %)	46 (90.2%)	43 (79.6%)		
Education (no. %)				
Minimal (illiterate/primary)	5 (9.8%)	4 (7.4%)	Chi-square test	*P*=.95
Secondary	17 (33.3%)	19 (35.2%)		
Technical training	8 (15.7%)	10 (18.5%)		
University	21 (41.2%)	21 (38.9%))		
Females skin coverage (no. %)				
Large (Hijab or Niqab)	41 (80.4%)	39 (72.2%)	Chi-square test	*P*=.33
Moderate (Western style)	10 (19.6%)	15 (27.8%)		
Employment (no. %)				
Unemployed	31 (60.8%)	28 (51.9%)	Chi-square test	*P*=.36
Indoor job	20 (39.2%)	26 (48.1%)		
Outdoor job	0	0		
Hands coverage (no. %)				
Yes	5 (9.8%)	4 7.4%)	Chi-square test	*P*=.66
No	46 (90.2%)	50 (92.6%)		
Medications (no %)				
Yes	14 (27.5%)	13 (24.5%)	Chi-square test	*P*=.73
No	37 (72.5%)	40(75.5%)		
Diseases (no %)				
None	33 (64.7%)	36 (66.7%)		
Yes DM (types 1 and 2), cancer, autoimmune diseases, bone diseases (osteoporosis, osteomalacia, and osteopenia), muscle weakness, lung function and wheezing, CKD (stages1, 2, 3), cardiovascular disease	18 (35.3%)	18 (33.3%)	Chi-square test	*P*=.83

DM: Diabetes mellitus; CKD: Chronic kidney disease.

600 000 IU of vitamin D2 and 500 000 IU of vitamin D3 is provided in **Tables 2 and 3**, respectively.

The influence of a single bolus dose of 600 000 IU vitamin D2 on the ratio of 25(OH) D3:D2 metabolites in 37 of 51 subjects was studied. All values below the limit of quantification (<4 ng/mL) were excluded. A total of 28 subjects (75.7%) showed a negative change, with a mean decrease of 6.75 ng/mL in the serum 25(OH) D3 level. However, 9 subjects (24.3%) displayed a positive change, with a mean increase of 4.47 ng/mL in the 25(OH)D3 level. Treatment with 600 000 IU vitamin D2 decreased 25(OH)D3 levels by a mean of 4 ng/mL in all subjects (n=37).

DISCUSSION

Several studies have evaluated the efficacy and safety of high-dose vitamin D regimens for correcting vitamin D deficiency.[27-31] In the present study, the patients supplemented with 500 000 IU vitamin D3 had a significant increase in their serum 25(OH)D level, compared with those supplemented with a single mega-dose of 600 000 IU vitamin D2. In the vitamin D3–treated group, the average total serum 25(OH)D level increased by 47.03 (23.67), and more than 92.6% (50/54) of subjects reached the optimal vitamin D status (25(OH)D ≥30 ng/mL) over 36.9 (2.9) days. Conversely, in the vitamin D2–treated group, only 8% (4 subjects) achieved optimal levels. Furthermore, only 40 % (20/51) attained a level ≥20 ng/mL in the vitamin D2 group, whereas 96.3% (52/54) of subjects attained a level ≥20 ng/mL in the vitamin D3 group.

The results obtained with the vitamin D3–treated group in this study are comparable with previous studies that applied the 10-day 50 000 vitamin D3 regimen. Hackman et al[30] showed that ≥90% of subjects treated with 500 000 IU achieved levels of >20 ng/mL. Bacon et al[28] showed that 500 000 IU is safe and effective in older women with serum 25(OH)D levels <10 ng/mL, and that it produces a 15% reduction in PTH concentrations. Wu et al[25] demonstrated that the high-dose regimen is safe and effective in raising mean serum 25(OH)D levels by 13 (4) ng/mL from baseline after 4 months.

However, the mean increment of serum 25(OH)D following supplementation with a single bolus dose of 600 000 IU vitamin D2 was only 10.33 (5.68) ng/mL over 43.08 (2.81 days. The 600 000 IU vitamin D2 single dose failed to correct vitamin D deficiency in 62% of subjects (31/51). Furthermore, serum 25(OH)D levels in 10% of subjects (5/51) remained ≤10 ng/mL.

The influence of a vitamin D2 mega-dose on 25(OH)D3 levels was studied. The level of 25(OH)

D3 metabolite increased in 24.3% of studied subjects (9/37); however, the increment in 25(OH)D3 level was modest (4.47 ng/mL), whereas the 25(OH) D3 level decreased in 75.7% (28/37) of subjects. The average decrease in 25(OH)D3 level (6.75 ng/mL) in 28 subjects in the vitamin D2–treated group was consistent with prior reports.[18,31,32] The mechanism(s) and potential importance of this remain unclear. It is possible that this decline simply reflects competition for available 25-hydroxylase activity; however, in vivo regulation of vitamin D 25-hydroxylation in humans is not entirely understood.33 Of more importance is the impact of a vitamin D2-induced reduction in circulating 25(OH)D3 on clinical outcomes. To the best of our knowledge, there is no evidence that suggests that 25(OH)D2 has different biological effects than 25(OH)D3. The mechanism(s) by which vitamin D2 administration decreases 25(OH)D3 levels and the clinical importance of this, if any, requires elucidation.

The findings of this study reveal that vitamin D2 when given as a single 600 000 IU dose was not effective in correcting the vitamin D status. It is possible that the administration of such mega-doses interferes with homeostatic control mechanisms, possibly hepatic, and induces a competition for available 25-OH hydroxylase activity. This may lead to a decrease in the efficiency of vitamin D2 conversion to its active hydroxymetabolites. Nevertheless, studies that used a total of 600 000 IU of vitamin D2 (12 doses of 50 000 IU) over a period of 4 weeks showed that all individuals in the vitamin D2–treated group achieved a serum 25(OH)D concentration above 30 ng/mL, a commonly recommended goal of vitamin D repletion therapy.[31] Another study, demonstrated that 500 000 IU vitamin D2 over 5 weeks was effective in increasing the 25(OH)D level by 24 ng/mL from baseline.[27] This may imply that vitamin D2 when given in weekly doses is more effective than if it is given in a single bolus dose of 600 000 IU.

The half-life of 25(OH)D in serum is about 22 to 28 days. Thus, the period of this study is equivalent to 1 to 2 half-lives for the 2 treatment groups. However, a minimum period of 3 to 4 half-lives is necessary to accurately study steady state levels.[30] Thus, results obtained in this study may not correspond to levels at the steady state. Instead, they may reflect the change in serum 25(OH)D following the 2 high-dose regimens.

This study provides data from patients coming through a clinical service, and is not a formal, randomized trial with a comparison group. Despite this, it was believed that the data were a valid representation of the effects of the vitamin-D dosing regimens used.

Table 2. Vitamin D status of 54 subjects after treatment with 500 000 IU vitamin D3.

Total post 25(OH) D (after Rx)	Number	%
≥20 ng/mL	52	96.3
≥30 ng/mL	50	92.6
≤10 ng/mL	0	0
10-<20) ng/mL)	2	3.7
>20 and less than 30 ng/mL	2	3.7

Table 3. Vitamin D status of 51 subjects after treatment with 600 000 IU vitamin D2.

Total post 25(OH) D (after Rx)	Number	%
≥20 ng/mL	20	40
≥30 ng/mL	4	8
≤10 ng/mL	5	10
10-<20) ng/mL)	26	52
>20 and less than 30 ng/mL	15	30

This study may have the following limitations. First, the study was conducted in an open-label design. In addition, the claims of the participants could not confirm that they were 100% compliant, although they were urged to be adherent, and were provided comprehensive counseling and education on the biological significance of vitamin D and its role in disease prevention. Second, this study had no placebo-only group. Not providing any vitamin D treatment to people who were deficient was considered unethical, especially given that 91.4% of the participants had 25(OH)D levels <12 ng/mL, suggesting they had "severe vitamin D deficiency". Since clothing can prevent sun exposure, and thus vitamin D synthesis and status, Mulla et al showed that females dressing in Hijab or Niqab have lower 25(OH)D plasma levels than their counterpart Western style-dressed females living in Jordan. In addition, sun exposure to uncovered face and hands as in Hijab-dressed females is not sufficient for vitamin D synthesis.[34] It is, therefore, possible that some of the changes in 25(OH)D levels were caused by factors other than the interventions provided, such as altered behavior relating to sun exposure or dietary modification. If this was the case, it is likely that the effect would be consistent across the 2 treatment groups. Furthermore, it is unlikely that increased ultraviolet exposure would have affected the results relating to changes in serum 25(OH)D levels,

since most of the participants of this study were women who wore conservative–style dress, shielding most of their skin, worked indoors or were housewives who had limited sun exposure.

The study sample size was sufficient. It included 109 treated subjects, from which 4 subjects were excluded following assessment, resulting in a final sample of 105 subjects. All participants fulfilled the requirements of the study, and the response rate was 83.2 % (109 subjects responded, out of 131 potential candidates).

The effect of vitamin D on parathyroid hormone, phosphate, and calcium was not investigated in this study due to the limitation of resources.

The present study demonstrated that the 10-day vitamin D3 regimen rapidly normalized 25(OH)D to optimal levels in the majority of subjects. This high-dose regimen may be an effective and cheap alternative for patients with vitamin D deficiency.

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