Journal of Pharmacy Practice
2017, Vol. 30(2) 172-179

DOI: 10.1177/0897190015626334
journals.sagepub.com/home/jpp
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Vitamin D Dosing Strategies Among Jordanians With Hypovitaminosis D: A Randomized Controlled Trial

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Abstract

Objective: To compare between weekly and daily cholecalciferol in patients with hypovitaminosis D and to determine the optimal maintenance dose. **Methods:** Seventy-one volunteers with hypovitaminosis D were randomly assigned to 2 dose regimens: cholecalciferol 50 000 IU weekly for 8 weeks, then 50 000 IU monthly for 2 months (group A) and 7000 IU daily for 8 weeks, then 12 500 IU weekly for 2 months (group B). Cholecalciferol was stopped for 2 months and reintroduced as 50 000 IU bimonthly for group A and 50 000 IU monthly for group B. **Results:** Two months after therapy, the mean serum 25-hydroxyvitamin D (25(OH)D) level increased from 11.4 to 51.2 ng/mL and from 11.7 to 44.9 ng/mL in groups A and B, respectively ($P = .065$). The levels of 25(OH)D declined similarly in both groups during maintenance and after holding therapy. After resuming cholecalciferol, 25(OH)D levels increased to 33.8 and 28.8 ng/mL in groups A and B, respectively ($P = .027$). There was a negative correlation between serum 25(OH)D levels and body mass index (BMI; $P = .040$). **Conclusion:** Timing and frequency of the dosing (daily vs weekly) have no effect on the rise in serum 25(OH)D levels as long as the accumulative dose of cholecalciferol is similar. Cholecalciferol 50 000 IU bimonthly is required to maintain sufficient 25(OH)D levels.

Keywords

hypovitaminosis D, cholecalciferol, therapy, Jordan

Introduction

Vitamin D is considered one of the important micronutrients in the body for its well-established role in bone and mineral metabolism.[1] Beyond its effects on the bone and neuromuscular functions, the finding of universal expression of vitamin D receptor in different tissues was an indicator that vitamin D is physiologically needed in these tissues.[1,2] Several studies explored the extraskeletal association of vitamin D and different aspects of health outcomes.[3] In humans, the increased risk of neoplasia, metabolic disorders, cardiovascular diseases, and immune dysfunction as multiple sclerosis was correlated with vitamin D deficiency.[4-7] Far beyond that, several trials addressed the association between vitamin D deficiency and mortality, but a causal relationship has yet to be established.[8,9]

In updated overview of global vitamin D status, the highest prevalence of vitamin D deficiency was found in neonates, children, adolescent girls, and women from the Middle East.[10] At a 25-hydroxyvitamin D (25(OH)D) cutoff <20 ng/mL, the prevalence of vitamin D deficiency among adults ranged between 40% and 90% in Lebanon, Saudi Arabia, occupied Palestine/Israel, Qatar, Tunisia, Morocco, and Iran.[11-17]

Jordan is one of the Eastern Mediterranean sunny countries that lies between latitudes 29°19 N and 32°35 N, in which ultraviolet B (UVB) radiation exposure should be sufficient for optimal concentrations of 25(OH)D. Surprisingly, vitamin D deficiency is highly prevalent in this country.[18-25] The prevalence of vitamin D deficiency was 94.1% in newborns, 28% in toddlers, 19.8% in preschool children, and 60.3% among nonpregnant Jordanian women of reproductive age.[18-21] In a national community-based study by Batieha et al, which included 5640 participants older than 18 years as a representative sample from all governorates in Jordan, the prevalence of

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vitamin D deficiency was 37.3% and 5.1% in females and males, respectively.[22]

For cultural and religious reasons, women in Jordan are wearing hijab (a dress style covering the whole body sparing the hands and face) and to a lesser degree niqab (a dress style covering the whole body except the eyes), and others have Western dress style. These clothing styles may make sun exposure less efficient.[21-24] In addition, dietary sources rich in vitamin D such as oily fish are not part of the usual diet consumed by Jordanians.

Also, the darker skin texture of the Middle Eastern population, which reflects high melanin production in response to ultraviolet radiation, could be another contributor to vitamin D deficiency.[26] Still the genetic architecture underlying vitamin D deficiency as single-nucleotide polymorphism in vitamin D-binding protein gene and vitamin D receptor gene has to be determined in Jordanians.[27,28] In June 2010, following the completion of data collection for the 2010 Micronutrient Survey, the Ministry of Health formally added vitamin D to the existing premix supplied to wheat flour to overcome the long-term musculoskeletal and metabolic effects of hypovitaminosis D.[29]

Serum 25(OH)D is the barometer of vitamin D status in the body. Still no consensus is reached on the optimal serum 25(OH)D level; the Institute of Medicine (IOM) considered that a serum 25(OH)D of 20 ng/mL is optimal for bone health.[30] On the other hand, the Endocrine Society affirmed that a serum 25(OH)D level $\geq$30 ng/mL is linked to increased health benefit, reduction in noncalcemic effects of vitamin D deficiency, maximal calcium absorption, and optimal reduction in parathyroid hormone (PTH) levels.[31]

Several dosing strategies and vitamin D forms were used for the treatment of vitamin D deficiency.[32] Worldwide, there is controversy about the appropriate vitamin D dose that maintains 25(OH)D levels $\geq$30 ng/mL. During follow-up of our patients, we didn't find the optimal vitamin D dose that can achieve sufficient 25(OH)D levels. Consequently, the present study attempts to determine the optimal maintenance dose that maintains 25(OH)D level $\geq$30 ng/dL and whether daily administration of vitamin D3 (cholecalciferol) offers any advantage over weekly vitamin D3 in the treatment of vitamin D deficiency.

Methodology

This study design was an open-label, randomized clinical trial. It took place between March 2012 and January 2013. The researchers invited employees of the National Center for Diabetes, Endocrinology and Genetics (NCDEG), Amman, Jordan, to volunteer in this study. Ninety-four employees accepted to participate in this study. Seventy-one of them met the inclusion criteria and had 25(OH)D level <30 ng/mL. Using simple randomization procedure, participants were assigned to 2 dose vitamin D regimens: cholecalciferol 50 000 IU weekly capsules for 8 weeks and then 50 000 IU monthly capsules for 2 months (group A) and 7000 IU daily capsules for 8 weeks and then 12 500 IU weekly capsules for 2 months (group B). Thirty-seven participants were allocated to group A treatment protocol, and the remaining 34 were allocated to group B treatment protocol (Figure 1).

Then, study participants in both treatment groups did not receive cholecalciferol therapy for 2 months. Finally, cholecalciferol therapy was resumed during which 50 000 IU every 2 weeks was given to group A participants (n = 30) and cholecalciferol 50 000 IU monthly to group B participants (n = 28) for another 3 months. Cholecalciferol was given by the researcher under direct supervision to ensure compliance.

There are 2 naturally occurring sources of vitamin D, either from sunlight exposure or from dietary sources such as oily fish. Other sources are fortified food products as flour, dairy products, orange juice, and cereals. Vitamin D3 is manufactured through ultraviolet irradiation of 7-dehydrocholesterol from lanolin and vitamin D2 through ultraviolet irradiation of the yeast sterol and ergosterol.[32]

Both ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) are used worldwide to treat and prevent hypovitaminosis D. However, the rationale behind using cholecalciferol in our study is due to its superior potency and longer duration of action.[33]

Well-trained health workers collected data from study participants regarding sociodemographic characteristics, dress style, milk intake, and exercise. To calculate body mass index (BMI), weight was measured in kilograms (to the nearest 0.5 kg) by a digital scale that was placed on a solid hard surface, and the subjects were asked to wear light clothes and take off their shoes. Height was measured by a stadiometer, with subjects standing in an erect position, heels on the hard floorboard, with the back facing the stadiometer vertical backboard. The shoulder blades, head, and buttocks were positioned to become in touch with the stadiometer vertical backboard.

Nonfasting blood samples (10 mL) were collected from participants in plain plastic colorless vacuum tubes for the analysis of serum 25(OH)D, PTH, calcium, and phosphorus at each stage of the study. Safety was assessed during this study through enquiry about signs and symptoms of vitamin D intoxication and serial measurements of serum calcium and 25(OH)D level.

Inclusion and Exclusion Criteria

Any NCDEG employee with 25(OH)D level <30 ng/mL was eligible to be included in this study. Pregnant women, subjects with chronic kidney disease, celiac disease, ulcerative colitis, and Crohn disease, and subjects already receiving vitamin D supplements were excluded from this study.

Measurement of 25(OH)D

Serum 25(OH)D was measured by ARCHITECT 25-OH vitamin D assay, which is a chemiluminescent microparticle immunoassay in human serum and plasma for the quantitative determination of 25(OH)D and is a trademark of Abbott Laboratories (IL, USA). The intra- and interassay coefficients of variation were 9% and 11%, respectively. PTH was measured by the electrochemiluminescence immunoassay, which is intended for use on Elecsys and Cobas immunoassay analyzer.

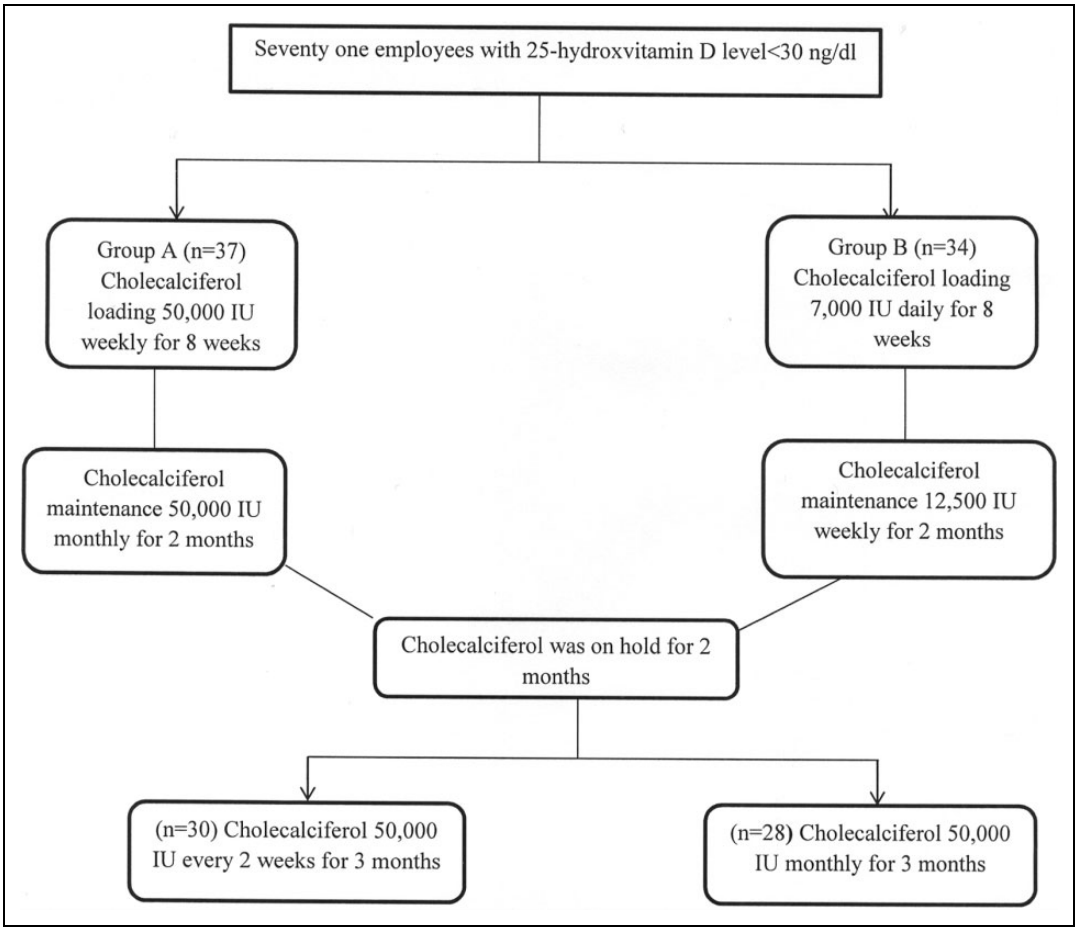

Figure 1. Study protocol.

Definitions of Study Variables

According to the definition of the Endocrine Society, vitamin D3 deficiency was defined as 25(OH)D <20 ng/mL, insufficiency as 25(OH)D of 21 to 29 ng/mL, and serum 25(OH)D levels $\geq$30 ng/mL indicate vitamin D sufficiency in our study protocol.[31]

PTH was considered normal if the level is between 9 and 55 pg/mL. BMI was defined and calculated according to the World Health Organization formula: weight in kilograms/(height in meters)^2.

Ethical Considerations

Ethical approval was taken from the Institutional Review Board at the NCDEG, Amman, Jordan. All subjects were verbally informed about the study protocol. They provided verbal consent for their participation, and no written consent was required. Participants were able to withdraw from the study at any time. Identifying information was kept strictly confidential. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

SPSS software program (version 21; SPSS incorporation, Chicago, Illinois) was used for data analysis. The statistical test used for the correlation analysis was Pearson correlation test. The study variables were compared using *t* tests for continuous variables and χ^2 test for categorical variables. *P* values less than .05 were considered statistically significant. Univariate analysis was accomplished to compute frequency distribution for all study variables. Multivariate analysis was used to identify the adjusted effect of study variables on 25(OH)D levels at the end of the study.

A sample size of 70 subjects was estimated to provide a study power of 90% and to detect 0.79 effect size in 25(OH)D mean difference between the 2 groups. The effect size was calculated using the following Cohen's formula: $d = \mathrm{I}\bar{x}_1 - \bar{x}_2\mathrm{I}/\sqrt{\sigma_1^2 + \sigma_2^2/2}$, where x_1 and x_2 are the means of group A and group B, respectively, and σ_1^2 and σ_2^2 are the variances of group A and group B, respectively.

Results

Participants were randomized to group A (n = 37) and group B (n = 34) treatment protocol. Of the 37 participants in group A, 30 completed the 4 stages of the study. Reasons for withdrawal included pregnancy (2 subjects) and leaving their work at the NCDEG (5 subjects). Of the 34 participants in group B, 28 completed the 4 stages of the study. Reasons for withdrawal

Table 1. Baseline Characteristics of the Study Subjects by Group (N = 71).

Variable	50 000 IU D3 dose group (group A; n = 37)	7000 IU D3 dose group (group B; n = 34)	*P*
Age (mean ± SD; n = 70), years	28.7 ± 5.1	28.6 ± 3.6	.948
Gender			.812
Female	23 (53.5%)	20 (46.5%)	
Male	14 (50.0%)	14 (50.0%)	
BMI (mean ± SD; n = 70)	24.6 ± 4.5	26.1 ± 4.8	.200
Marital status			.909
Single	18 (51.4%)	17 (48.6%)	
Married	19 (52.8%)	17 (47.2%)	
Smoking status (n = 70)			.781
Current smokers	8 (47.1%)	9 (52.9%)	
Nonsmokers	29 (54.7%)	24 (45.3%)	
Milk consumption			.875
Daily	9 (56.3%)	7 (43.8%)	
Weekly	16 (53.3%)	14 (46.7%)	
Can't tolerate	12 (48%)	13 (52%)	
Dress style for females			.286
Hijab	21 (56.8%)	16 (43.2%)	
Western style	2 (33.3)	4 (66.7%)	
Exercise status (n = 70)			.111
Regular	14 (70.0%)	6 (30.0%)	
Irregular	23 (46.0%)	27 (54.0%)	
25(OH)D level at baseline (mean ± SD), ng/mL	11.4 ± 5.1	11.7 ± 6.4	.825
PTH level at baseline (mean ± SD), pg/mL	30.5 ± 10.2	33.4 ± 12.7	.289
Baseline Ca (mean ± SD; n = 70)	9.8 ± 0.4	10.0 ± 0.5	.169
Baseline phosphorus (mean ± SD; n = 70)	3.8 ± 0.6	3.7 ± 0.4	.447

Abbreviations: BMI, body mass index; Ca, calcium; 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; SD, standard deviation.

Table 2. Changes in 25(OH)D and PTH Levels During Study Steps, According to Study Group.

	After loading for 2 months	After maintenance for 2 months	After holding therapy for 2 months	After resuming therapy for 3 months
Mean vitamin D level ± SD				
Group A (50 000 IU D3 weekly dose group)	51.2 ± 14.2	32.0 ± 6.9	26.3 ± 7.1	33.8 ± 8.0
Group B (7000 IU D3 daily dose group)	44.9 ± 14.5	29.1 ± 6.4	27.2 ± 6.0	28.8 ± 5.8
P	.069	.141	.589	.013
Mean PTH level ± SD				
Group A (50 000 IU D3 weekly dose group)	22.0 ± 7.2	33.8 ± 11.4	34.1 ± 9.8	33.7 ± 11.1
Group B (7000 IU D3 daily dose group)	28.7 ± 10.4	34.1 ± 12.1	33.9 ± 14.0	38.1 ± 11.0
P	.002	.914	.948	.145

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; SD, standard deviation.

included pregnancy (1 subject) and leaving their work at the NCDEG (5 subjects). Mean age of participants was 28.6 ± 4.4 years, mean BMI was 25.3 ± 4.7 kg/m^2, half of them were married, and 60% were females. Around 75% of the participants were not smokers, and only 28.2% of them stated doing regular exercise.

There was no significant difference between both study groups in baseline characteristics in terms of age, gender, BMI, smoking, marital and exercise status, milk intake, and dress style (Table 1). In addition, 25(OH)D and PTH levels at the baseline were not statistically different between both groups ($P = .825$ and $P = .289$, respectively; Table 1).

The mean baseline serum 25(OH)D levels were 11.4 and 11.7 ng/mL in groups A and B, respectively ($P = .825$). Serum 25(OH)D levels increased significantly after 2 months of cholecalciferol initiation in both groups ($P < .001$), reaching 51.2 and 44.9 ng/mL in groups A and B, respectively, with no significant difference between the study groups ($P = .069$).

No significant difference in 25(OH)D levels was observed, and both regimens were equally effective in raising serum 25(OH)D levels, except in the last step, when participants in group A were given cholecalciferol 50 000 IU every 2 weeks, whereas participants in group B were given cholecalciferol 50 000 IU monthly, at that point the first group had a significantly higher 25(OH)D level than the second group (33.8 and 28.8 ng/dL, respectively, $P = .013$).

On the other hand, PTH level was significantly lower in group A than in group B 2 months after cholecalciferol initiation (22.0 and 28.7 pg/mL, respectively, $P = .002$), but this difference between the 2 groups in PTH levels diminished in the rest of study protocol steps and become statistically not significant as shown in Table 2.

There was a statistically significant correlation between serum 25(OH)D level after reloading and cholecalciferol dose ($P < .001$), although a statistically significant negative correlation between serum 25(OH)D levels and BMI ($P = .040$) was observed as shown in Table 3. There was no statistically significant correlation between 25(OH)D level and age, gender, smoking status, calcium, and phosphorus levels (Table 3).

Discussion

Our findings revealed that daily and weekly doses of cholecalciferol were equally effective in raising serum 25(OH)D levels

Table 3. Study Variables and Their Correlation With 25(OH)D Level at the Final Step of the Study.

Variable	Pearson correlation coefficient	*P*
Age	−0.008	.956
Smoking status	−0.025	.858
BMI	−0.280	.040
Calcium level	+0.017	.901
Phosphorus level	+0.157	.256
Vitamin D3 dose 50 000 IU	+0.665	<.001
Female gender	+0.221	.108

Abbreviations: BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D.

after the first 2 months of cholecalciferol initiation, and the daily dose offers no advantage over the weekly dose. Therefore, timing and frequency of the dosing (daily vs weekly) have no effect on the rise in serum 25(OH)D levels as long as the cumulative dose of cholecalciferol was similar between the study groups. Thereby, the choice of the weekly dose can optimize individual's adherence.[34]

Comparable to our findings, 3 vitamin D3 protocols at 1500 IU daily, 10 500 IU once weekly, or 45 000 IU once monthly achieved statistically similar increment in serum 25(OH)D levels among 48 elderly women with vitamin D deficiency after 2 months of therapy.[35] Also, in United Arab Emirates, Saadi et al had shown that 60 000 IU monthly vitamin D2 is an effective alternative to 2000 IU daily vitamin D2 in nulliparous and lactating women with vitamin D deficiency.[36] Although Chel et al investigated the effect of equivalent doses of vitamin D3 600 IU daily, 4200 IU weekly, and 18 000 IU monthly in nursing home residents with hypovitaminosis D, after 4 months of therapy, daily vitamin D3 was significantly superior to weekly vitamin D3, but monthly D3 was the least effective in nursing home residents.[37] The inconsistency between the study by Chel et al and the current study findings can be related to the younger age-group of our study participants with less problems of absorption in the gut that is commonly found in the elderly.[38,39]

After the maintenance phase (ie, 2-month therapy of cholecalciferol 50 000 IU monthly and 12 500 IU weekly for participants in groups A and B, respectively), a significant decline in serum 25(OH)D levels was observed in both groups. Furthermore, holding vitamin D therapy results in further decline in serum 25(OH)D levels. Similarly, in a retrospective evaluation of 213 patients with a baseline serum 25(OH)D level <30 ng/mL who received different replacement strategies of ergocalciferol 50 000 IU, Bryant et al noticed that attainment of adequate vitamin D level depends on timing of posttherapy measurement of serum 25(OH)D. In 76% of patients who attained vitamin D sufficiency, their serum 25(OH)D level was measured less than 1 month after completing replacement therapy, whereas in 64% of patients who did not attain vitamin D sufficiency, their serum 25(OH)D level was measured between 1 and 3 months after completing replacement therapy ($P < .0001$). These findings highlight the importance of early assessment of serum 25(OH)D level after replacement, thus initiation of the required maintenance therapy.[40]

After reintroducing cholecalciferol therapy, the level of 25(OH)D increased to 33.8 and 28.8 ng/mL in those who received 50 000 IU D3 twice weekly and 50 000 IU D3 monthly, respectively ($P = .013$). Hence, our study participants need at least 3500 IU D3 daily to keep 25(OH)D ≥30 ng/mL, and this finding leads us to suggest that cholecalciferol 50 000 IU bimonthly is required to maintain sufficient 25(OH)D levels for maximal health benefits. The recommended maintenance daily dose of cholecalciferol in the current study is higher than that recommended by the IOM for adults,[30] also higher than that recommended by the Endocrine Society.[31] The plausible explanation for this finding is that the optimal dose of vitamin D supplement depends on many factors, including sunlight exposure, race/ethnicity, dietary intake, absorption, and metabolism.[38,41-43] However, the recommended maintenance dose in the current study is still lower than the tolerable upper intake level recommended by the Endocrine Society, which is 10 000 IU daily but approaching the tolerable upper intake level recommended by the IOM, which is 4000 IU daily.[30,31] Keeping in mind that 10 000 IU of vitamin D3 per day for up to 5 months do not cause toxicity, consequently, vitamin D toxicity is a remote possibility among study participants.[41]

The association between obesity and vitamin D deficiency has been strongly confirmed in previous studies.[37-39] This association can be caused by less sunlight exposure in obese individuals who may have less outdoor activity. Furthermore, vitamin D is a fat-soluble vitamin, deposited and stored in the fat compartments. Obese individuals have larger body surface area and more subcutaneous fat, therefore, the release of cutaneous synthesized vitamin D is affected, leading to lower serum 25(OH)D levels in the circulation.[44-47]

A statistically significant negative weak correlation between serum 25(OH)D levels and BMI ($P = .040$) was evident in the current study (Table 3). Ultimately, obese individuals require higher doses of vitamin D3 than lean individuals to achieve the same serum 25(OH)D levels. Holick et al assessed the impact of obesity on cutaneous production of vitamin D3 and intestinal absorption of vitamin D2. The increase in serum vitamin D level was 57% lower in obese in comparison to nonobese individuals 24 hours after whole-body irradiation. Moreover, there was an inverse correlation between BMI and peak serum 25(OH)D level after a challenge with 50 000 IU oral vitamin D2.[47]

Many studies clearly demonstrated the inverse relationship between PTH and 25(OH)D levels. Chapuy et al and Holick et al demonstrated that serum PTH concentrations started to rise when serum 25(OH)D concentrations fell below 30 ng/mL,[48,49] whereas others were unable to demonstrate a threshold at all.[50,51] Sai et al failed to establish a threshold of PTH suppression within the serum 25(OH)D range 6 to 60 ng/mL.[51] In our study, after 2 months of cholecalciferol therapy, PTH declined in both treatment groups but was significantly lowered in the group that received 50 000 IU weekly. Afterward, PTH level increased with no statistically

significant difference between the 2 groups. This finding can be explained by the variation in PTH levels according to age, sex, time of the day, and dietary calcium and phosphorous intake.[52-54]

Several implications arise from this study. First, cholecalciferol 50 000 IU monthly is inadequate in maintaining serum 25(OH)D levels ≥30 ng/mL. Second, no difference between daily and weekly dosing of cholecalciferol was found, if the cumulative dosing was similar. The weekly high-dose cholecalciferol might be more convenient and appropriate due to infrequent dosing intervals. Furthermore, over-the-counter preparations of cholecalciferol are inadequate in maintaining serum 25(OH)D level ≥30 ng/mL, and it is more likely that higher doses might be required than what is found in these preparations.[55,56] Moreover, it is the first study in the Eastern Mediterranean region and Jordan that assessed the effect of cholecalciferol on serum 25(OH)D levels with follow-up to determine the maintenance dose that keeps up sufficient vitamin D stores.

As part of the aging process, the ability to synthesize vitamin D in the skin is diminished.[57] Thereby, elderly need higher doses of vitamin D3 for repletion of vitamin D status in comparison to young adults.[38] However, our study participants were younger than 40 years; further large-scale study is needed to determine the requirements of vitamin D supplements among elderly in Jordan.

Although vitamin D toxicity is rare, further long-term study is needed to address the safety of twice-monthly 50 000 IU cholecalciferol in maintaining sufficient serum 25(OH)D levels. It is the first study that assessed the effect of cholecalciferol on serum 25(OH)D levels for the first time in this region and for the first time on a Jordanian population. In addition, it followed the 25(OH)D level not only after the first loading dose but also it followed for a maintenance period and for a reloading period too.

There are some limitations to the current study. Although dietary assessment was done initially at the time of enrollment, further systemic dietary assessment all through the study was not carried out, which could potentially affect serum vitamin D levels. Furthermore, work site (indoor or outdoor) was difficult to control, which could also affect the serum vitamin D level. In addition, this trial was an open-label trial, and this might introduce a possible bias.

Our findings may help guide the health care professionals in Jordan to use the appropriate dosage to treat and maintain adequate vitamin D level, and we believe further large-scale studies are needed to confirm and generalize our results.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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