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Comparison of Monthly and Weekly Doses of Cholecalciferol in Treatment of Perimenopausal Women with Vitamin D Deficiency

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ABSTRACT

Background: Women in their perimenopausal period should have an optimal vitamin D level. This study compared monthly versus weekly doses of cholecalciferol in treatment of perimenopausal women with vitamin D deficiency.

Methods: Eighty 42-57 years old women with vitamin D deficiency were enrolled. Half of the patients received bolus monthly oral doses and the other half of patients received weekly oral doses for four months. The vitamin D level was determined at the end of each month and one month after the end of the period of treatment. Demographic and biochemical data were analyzed too.

Results: Demographic information indicated absence of any significant difference between the two treatment groups. Serum level of 25(OH)D3 in the monthly group ranged from 11.5±2.6 ng/mL to 48.6±4.8 ng/mL from baseline to day 111, whereas those in the weekly group ranged from 10.3±3.1 ng/mL to 46.9±6.3 ng/mL. On days 27, 55, 83, 111, and 150, there was no discernible difference in the fluctuations of 25(OH) D3 level between the two treatment groups; while the mean change from baseline between the two groups only became significant on day 13. Between baseline and day 150, no significant alteration happened for biochemical markers.

Conclusion: Weekly and monthly vitamin D dosages were equally effective in restoring normal level of 25(OH) D3 in perimenopausal women with vitamin D deficiency.

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Introduction

The role of vitamins on health status and survival of cells have been described before. Among vitamins, low vitamin D level is common that can lead to some health issues, primarily affecting the bones and muscles (1-3). The body status for vitamin D level has been linked to an optimal immune function, cardiovascular diseases, cancer prevention, difficulties in losing weight, and even neurological and mental diseases (4-8). Women, children, and the elderly are more likely to be vitamin D deficient in the general population (1).

Despite sunny weather in most of the months of the year, vitamin D deficiency is still common in the Middle East countries including Iraq with women being the most affected group of the population (9-12).

Perimenopausal women, in particular, should have an optimal vitamin D level as many recent studies showed its contribution to a healthier menopause and its positive effect on mood, vaginal health, and bone density (13-16). Despite the great controversy about the optimal level of serum 25(OH) D3 which is required to maintain normal physiological and biochemical bone health, a target concentration of 30 ng/mL is recommended by the majority of the studies (17). Most guidelines recommend a daily dose ranging from 600 to 2000 IU per day to reach target levels and higher doses are required for those who are at an increased risk of vitamin D deficiency (18). A lot of factors affect the achievement of target blood levels of vitamin D with treatment including patients' dietary habits and compliance to treatment. According to many studies, most patients find it difficult to adhere to daily doses of vitamin D (19, 20), and since 25(OH) D3 has a half-life of two to three weeks, regimens of weekly or monthly doses have been widely used to ensure better patients' adherence to treatment (21). Although numerous published researches have compared vitamin D supplementation regimens on a daily, weekly, and monthly basis (22-26), the ideal dosing frequency that better achieves target levels is still controversial (12), There are currently few researches addressing the most effective treatment plans for them. The current research aimed to identify the effect of weekly and monthly dosing intervals of the necessary vitamin D dosages to achieve target levels of 25(OH) D3 in perimenopausal women in Basrah, Iraq, who were vitamin D deficient.

Materials and Methods

This is a randomized tow-arm interventional study conducted during the period from October 2022 to March 2023. The study comprised a total of 80 women with vitamin D deficiency, aged 42–57 years, who visited the outpatient clinic at Basrah Teaching Hospital in Basrah, Iraq. A blood 25(OH) D3 concentration of less than 20 ng/mL was considered as vitamin D insufficiency (17). All women filled out a questionnaire form including full medical history and socio-demographic data with a written informed consent. The study did not include women who had a history of cardiovascular, endocrine, renal, neoplastic, or gastrointestinal diseases, or who had used vitamin D supplements in any form within the previous six months.

The 80 women were divided into two equal groups and administered vitamin D either weekly or monthly for four months. The monthly dosage of vitamin D was to maintain the target level of 25(OH) D3 above 30 ng/mL based on mean weight and baseline blood level of 25(OH) D3 (27). The total calculated doses were divided into either 4 weekly oral doses or one bolus oral monthly dose according to the patient group. Weekly doses were equal to 25000 IU and the monthly doses were equal to 100000 IU. Both patients' groups received a total cumulative dose of 400000 IU during the four months of therapy. All doses were given in the form of an oral solution (DIBASE ®ABIOGEN Pharma S.p.a, Italy). All patients were advised to take the doses mixed with a diary drink.

Blood samples were collected at baseline, days 13, 27, 55, 83, 111, and day 150 which corresponded to one month after the end of the period of treatment. The levels of 25(OH) D3, calcium, albumin, phosphate, creatinine, and parathyroid hormone (PTH) were measured in the serum. The Roche biochemical analyzer (®Roche Diagnostics, Germany) was used for the biochemical analysis. Serum level of 25(OH) D3 was measured using high-performance liquid chromatography (HPLC), by the standard procedure set by the National Institute for Standards and Technology (NIST) and the Center for Disease Control and Prevention (CDC) (28, 29). Every participant finished the therapy term, and the empty prescription containers were gathered to verify compliance. For statistical analysis, IBM SPSS® software (version 26, Chicago, IL, USA) was utilized. The hypothesis of changes for repeated measures relative to baseline values was evaluated using the conventional paired t-test and a p value of less than 0.05 was considered statistically significant.

Results

The study participants' demographic data was shown in Table 1. There was no significant difference between the two groups' baseline demographic data (p>0.05) (Table 1). The two subject groups' baseline serum levels of 25(OH) D3 were comparable (p=0.77). As anticipated, the monthly group's serum 25(OH) D3 concentrations increased sharply, with mean levels surpassing 30 ng/mL on day 13. Day 27 showed a modest reduction in 25(OH) D3 level, although they were still more than 30 ng/mL. Levels continue to rise following the second, third, and fourth monthly doses at days 55, 83, and 111, respectively, and reached the mean levels of over 45 ng/mL on day 111. Day 150, which was 59 days following the last monthly dosage, was when 25(OH) D3 levels started to decline; but still stay more than 30 ng/mL.

Table 1: Demographics data of the study participants.

Variable	Weekly regimen n=40	Monthly regimen n=40
Age (year) Mean±SD	47.8±5.5	48.4±6.7
BMI (kg/m2) Mean±SD	29±3.2	30±2.8
Smoking (n/%)		
Smoker	4 (10%)	6 (15%)
Non-smoker	37 (90%)	34 (85%)

BMI: Body mass index; SD: Standard deviation.

The weekly group's 25(OH) D3 blood levels increased gradually, reaching around the same levels on days 27, 55, and 83. The weekly group's 25(OH) D3 concentration was higher than the monthly group on day 111, even though the difference was not statistically significant (p=0.65). On day 150 (38 days after the last weekly dose), 25(OH) D3 level tend to decrease, but they remained at more than 30 ng/mL, which was similar to the monthly group. The monthly dosing group's mean level of 25(OH) D3 was 11.5±2.6 ng/mL at the beginning of the study and 48.6±4.8 ng/mL on day 111, with a mean change from baseline of 28.7±6.7 ng/mL (p<0.0001).

There was a dramatic rise in 25(OH) D3 concentration after the first monthly dose, while the mean changes from baseline between the two groups did not differ significantly after day 27 (p>0.05), with the sole significant difference occurring on day 13 (p<0.05). On day 150 which corresponded to one month after the end of the period of treatment, blood concentration of 25(OH)D3 tended to decrease; but the mean concentration remained above the target level of 30 ng/mL in both treatment regimen groups (Figure 1). During the period of therapy, no significant medication-related side effects were reported in both treatment regimen groups. Regarding other related biochemical laboratory parameters, no significant changes in serum level from baseline were observed during the period of treatment in both treatment regimen groups (p>0.05) (Table 2).

Discussion

Nutrients and vitamins play pivotal roles in cell proliferation and growth and finally can provide a healthy status for the individual (30, 31). Among vitamins, vitamin D status has a crucial influence in healthy adults (32). To determine the ideal dose schedule that produces the optimum vitamin D3 status,

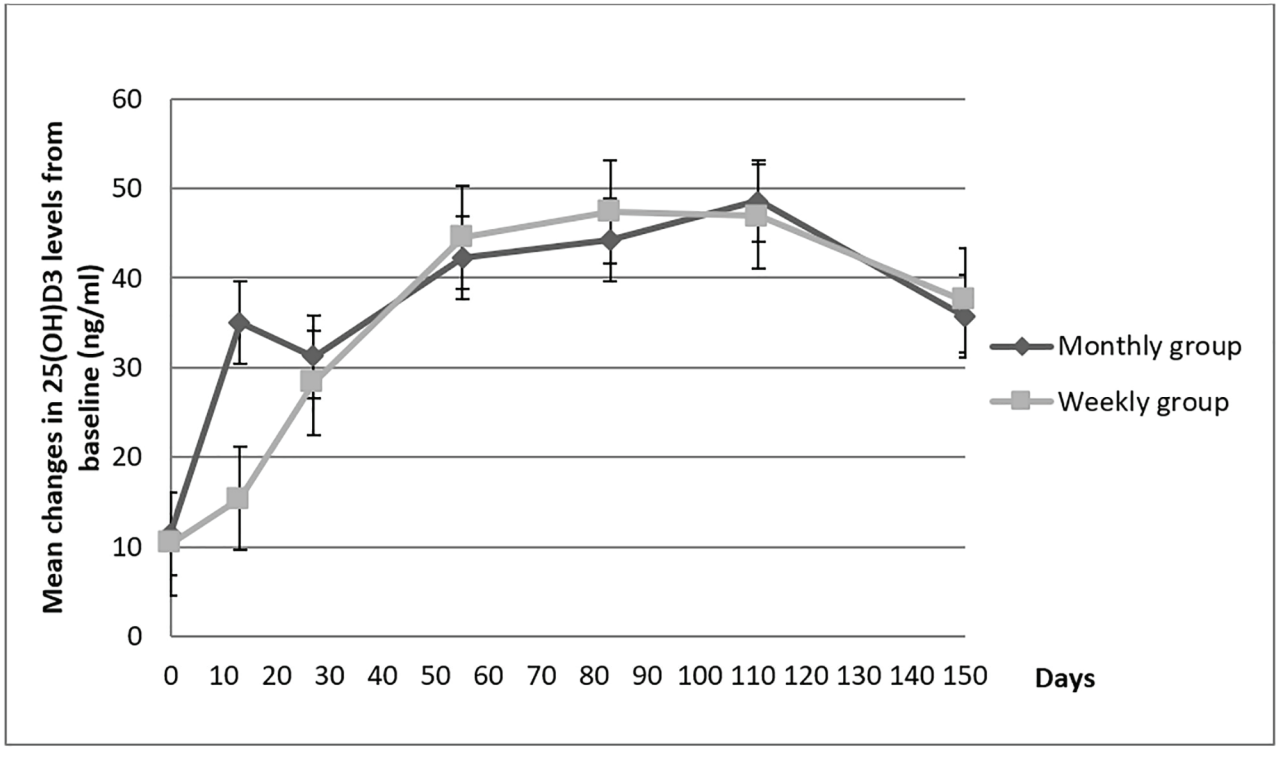

Figure 1: Mean changes in 25(OH) D3 serum level in both monthly and weekly dosing groups over time. Error bars represent a 95% confidence interval being only significant on day 13 (p<0.05).

Table 2: Changes in serum level of related biochemical parameters in the study groups over time.

Biochemical parameter	Weekly regimen (Mean±SD)	Monthly regimen (Mean±SD)
Corrected Calcium (mg/dL)		
Baseline	8.8±0.6	8.4±0.4
Day 150	8.7±0.5	8.6±0.4
Change from baseline*	0.0±0.2	0.0±0.2
Phosphate (mg/dL (		
Baseline	3.1±0.5	3.41±0.6
Day 150	3.1±0.6	3.4±0.5
Change from baseline*	0.0±0.3	0.0±0.6
Alkaline phosphatase (IU/L)		
Baseline	77.4±16.2	78.6±15.2
Day 150	77.6±16.4	78.4±15.4
Change from baseline*	0.7±6.5	0.4±5.3
PTH (ng/L)		
Baseline	19.3±8.3	20.2±11.6
Day 150	17.6±8.1	21.3±10.2
Change from baseline*	1.8±5.8	2.2±8.3
Creatinine (mg/dL)		
Baseline	0.7±0.1	0.7±0.2
Day 150	0.7±0.1	0.8±0.2
Change from baseline*	0.0±0.2	0.0±0.2

*p>0.05 between treatment groups.

this study compared weekly and monthly vitamin D3 dosing regimens for the treatment of perimenopausal women with vitamin D3 shortage. Following four months of treatment, both treatment regimens of 25(OH) D3 levels returned to baseline with equal success when weekly or monthly vitamin D3 dosages were administered. Both weekly and monthly dosing schedules were effective in reaching the target level of 25(OH) D3, as evidenced by the mean levels of 25(OH) D3 in both treatment groups exceeding 30 ng/mL.

After treatment was stopped, the level of 25 (OH) D3 was maintained above 30 ng/mL for four months. No drug-related side effects were identified, and other serum biochemical markers that controlled bone were unaffected by the comparatively large doses of vitamin D3 employed for the patients. Our findings revealed that the total monthly calculated dosages of vitamin D3 were equally safe and effective in restoring and maintaining normal 25(OH)D3 level, regardless of whether they were given as a monthly bolus dosage or divided into four weekly doses.

The results of our study are in agreement with those of other studies. By comparing weekly and daily dosages of cholecalciferol,it was shown that treatment of vitamin D insufficiency in patients for two months were equally successful in bringing 25(OH)D3 level back to normal after the end of the two months (33-35). In our study, treatment was continued for four months and doses of cholecalciferol were relatively high, even one month after stopping treatment, 25 (OH) D3 level was still above target level of 30 ng/mL. When monthly and daily vitamin D administration for two months was compared, it was shown that both dosing strategies were equally effective in raising vitamin D level to 20 ng/mL. However, the mean level of 25(OH) D3 in both treatment groups fell short of the target level of 30 ng/mL, perhaps as a result of the study's relatively low cholecalciferol dosages (25). When daily, weekly, and monthly administration of vitamin D for three months were compared by use of a target level of 20 ng/mL, it was shown that low doses of cholecalciferol in three regimens were equally safe and effective in reaching the target vitamin D level of 30 ng/mL (25). In a two-month study, the effect of daily, weekly, and monthly vitamin D supplementation on a group of patients with hip fractures was compared and the findings revealed that all three regimens similarly achieved the necessary vitamin D level of 30 ng/mL (24).

It was found that monthly dosing intervals were less effective than weekly and daily regimens with the daily dosing regimen being the most effective. The three dosing regimens on nursing home resident elderly patients which ensured daily adherence to treatment and with the same cumulative doses in the three dosing interval regimens led to a discrepancy in the absorption of the medication between groups and explain the different results from other studies, even they did not use the same cholecalciferol drug formulation for all patients (19). Many studies have also recommended that the serum level of 25(OH) D3 is needed to be kept above 30 ng/mL to prevent fractures (2, 33-35), and perimenopausal women at

risk of osteoporosis and fractures (36-38). We have also reported that this group of women needs to be treated with higher doses of cholecalciferol and for longer durations to achieve desirable goals.

One limitation of this study was the small sample size as a lot of patients have been excluded because of chronic medical illnesses, and more studies may be required to identify if the same results can be applied to women with chronic illnesses like diabetes or thyroid diseases. Another limitation was that the patients had not been followed up after day 150 and it was not known whether the target level of 25(OH)D3 had been maintained after the last sample collection or not, so further studies with longer periods of follow up after discontinuation of treatment are required.

Conclusion

To restore normal level of 25(OH) D3 in perimenopausal women with vitamin D deficiency, we demonstrated that weekly or monthly doses of vitamin D were equally safe and effective. After stopping treatment, the level of 25(OH) D3 had to be maintained more than 30 ng/mL for four months. So, the choice of treatment dosing regimen for patients with vitamin D deficiency can be arranged according to patient preference and ability to adhere to long-term periods of supplementation.

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Authors' Contribution

Al-Mayyahi ZA: Main researcher, research idea, study design, sample size determination, data collection, results interpretation, and manuscript writing and reviewing. Abdul Reda EA: Assistant researcher, methodology, investigations, manuscript editing, and reviewing. Jaber AS: Assistant researcher, data collection, and manuscript editing and reviewing.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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