Original Article

Daily oral vitamin D_3 regimen in similar cumulative doses is more effective than weekly oral vitamin D_3 regimen in patients with vitamin D deficiency

Abstract

Context: Vitamin D deficiency is a common health problem worldwide, especially in the Middle Eastern region. Although various dosing regimens of vitamin D have been used for the treatment of vitamin D deficiency, it is still unclear as to which dosing regimen can efficiently increase the serum level of vitamin D in different patient population. **Aim:** This study was designed to compare the efficacy of weekly and daily regimens of vitamin D3 in patients with vitamin D deficiency. **Settings and Design:** A randomized clinical trial was conducted in the autumn and winter of 2016 and 2017, Hamadan, Iran. **Materials and Methods:** A total of 130 patients with moderate to severe hypovitaminosis D were allocated into two groups: weekly 50,000 IU (routine recommended dose for vitamin deficiency treatment) or daily 4,000 IU (safe upper limit dose of vitamin D per day) of oral vitamin D_3 for 8 and 14 weeks, respectively. The serum levels of 25-OH-vitamin D were measured in all patients at baseline and at the end of the treatment period. **Results:** Results of this study showed that though both dosing regimens can be effective in increasing the serum level of 25-OH-vitamin D, higher percentage of the subjects in the daily regimen group achieved the sufficient serum level of 25-OH-vitamin D when compared to the weekly regimen group. **Conclusion:** Accordingly, probably owing to better bioavailability of daily regimen of vitamin D_3 and establishment of a more steady serum concentration compared with weekly regimen, it can be recommended as the preferred dosing regimen for effective treatment of vitamin D deficiency.

Keywords: *Calciferol, calcium, 25-hydroxyvitamin D3, vitamin D, vitamin D deficiency*

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Introduction

Vitamin D deficiency is recognized as one of the major health problems that is increasing globally worldwide.[1] It is highly prevalent in all age-groups, especially among children, pregnant and postmenopausal women, and the elderly.[2,3] Despite the appropriate geographical locations (latitude and altitude) of Middle Eastern countries regarding sufficient sun exposure, due to their especial culture in clothing, which limits the cutaneous synthesis of vitamin D, high prevalence of vitamin D deficiency in the residents of this region of the world has been reported.[4,5] In addition, vitamin D–fortified foods that are designed to prevent vitamin D deficiency are not widely accessible for all residents in these countries.[6] The currently available literature on the Iranian population suggests that the prevalence of vitamin D deficiency in the Iranian community is very high and approximately 64% of women and 44% of men have vitamin D deficiency.[7]

The required amounts of vitamin D are supplied from food sources and cutaneous production following sufficient sun exposure. However, dietary intake of vitamin D nonsignificantly affects the serum level of vitamin D because only a few foods have a significant amount of vitamin D.[8] Therefore, several factors such as increased metabolism of vitamin D, insufficient dietary intake of vitamin D, reduced sun exposure, and decreased endogenous synthesis can lead to vitamin D deficiency.

Through various mechanisms such as increasing intestinal absorption of calcium and phosphorous and decreasing the elimination of calcium and phosphorous from kidneys, vitamin D is considered as an essential component for bone health and homeostasis and vitamin D deficiency is considered as one of the major causes of bone diseases.[9-11] Beyond its important role on the pathogenesis of musculoskeletal diseases,[12,13] current evidence has revealed a causal association between vitamin D deficiency and many non-musculoskeletal diseases such as various type of cancers,[14] respiratory infections,[15]

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cardiovascular diseases,[16] diabetes mellitus,[17] inflammatory bowel disease,[18] neurologic diseases,[19] and psychiatric disorders.[20] However, yet no convincing evidence that vitamin D supplementation can prevent or treat such diseases is available.

In spite of the high prevalence of vitamin D deficiency and its important consequences due to the absence of specific signs and symptoms, it may remain undiagnosed and untreated in the majority of patients.[21] Measurement of 25-hydroxyvitamin D (25(OH)D) is used for the estimation of vitamin D sufficiency. Although based on the Institute of Medicine (IOM) recommendation, the serum level of 25(OH)D above 30 ng/mL is defined as vitamin D sufficiency, but optimal serum level of 25(OH)D has not been defined clearly.[22,23]

Vitamin D is found in the following two forms: ergocalciferol (D2) and cholecalciferol (D3). Supplementation with cholecalciferol rather than ergocalciferol was recommended for the treatment of vitamin D deficiency because according to the results of some studies, cholecalciferol is more effective in increasing the serum level of 25(OH)D.[24] Multiple dosing regimens are suggested for the treatment of vitamin D deficiency. Although in routine clinical practice, weekly 50,000 IU of vitamin D3 for eight weeks is used for vitamin D replacement in vitamin D deficiency, no consistent data suggesting the ideal regimen of supplementation are available.[8] The efficacy of different dosing regimens of vitamin D has been evaluated in several studies, but due to heterogeneity of these studies, conflicting results have been reported.[25,26] In this regard, a study by Ish- Shalom *et al.* in the elderly women showed that daily, weekly, or monthly dosing frequencies of vitamin D supplementation are equally effective in increasing the serum level of 25(OH)D.[27] Inconsistent with these results, Chel *et al*., in their study, found that a daily dose of vitamin D supplementation could increase mean serum 25(OH)D levels more significantly than a monthly dose.[28] It seems that several factors such as age, sex, concomitant medication, comorbidity, pregnancy and lactation status, type and dosage form of vitamin D, and duration of treatment can affect the serum level of 25(OH)D after treatment with various regimens.

Owing to conflicting results concerning the efficacy of various regimens of vitamin D supplementation, this study was designed to compare the efficacy of 50,000 IU weekly oral vitamin D3 regimen (dosing regimen that was routinely prescribed for the treatment of vitamin D deficiency)[29] and 4,000 IU daily oral vitamin D3 regimen (safe upper limit dose of vitamin D per day)[30] in the treatment of patients with vitamin D deficiency.

Materials and Methods

Subjects and study design

This study was an open-labeled, randomized clinical trial study conducted in autumn and winter of 2016 and 2017 in Hamadan, Iran. Hamadan is a cold and mountainous city that is located in the western region of Iran. The study protocol was approved by the local ethics committee and it was registered in the Iranian Registry of Clinical Trials (IRCT2017022022965N6). All participants were given a written informed consent before enrollment to the study.

25(OH)D serum level was requested for 395 subjects to be screened for enrollment in the study. The serum level of 25(OH)D >30 ng/mL was considered as vitamin D sufficiency, and the serum level of 25(OH)D between 20–30 ng/mL, 10–20 ng/mL, and <10 ng/mL was considered as mild, moderate, and severe vitamin D deficiency, respectively. In addition to hypovitaminosis D, patients were included in this study if the following inclusion criteria were met at the baseline of the study: age above 18 years; body mass index (BMI) <30 kg/m^2; absence of hypo/hypercalcemia; hypo/hyperphosphatemia and primary, secondary, and tertiary hyperparathyroidism; no consuming high dose of calcium supplement (≥1200 mg/day of elemental calcium); absence of hepatic or renal impairment; no history of using medications that affect the serum level of 25(OH) D, such as phenytoin, phenobarbital, carbamazepine, and valproate sodium; absence of any comorbidity, which results in malabsorption including celiac disease, inflammatory bowel disease, and gastrectomy; absence of pregnancy or lactation; and no history of consuming glucocorticoids for at least six months before the study. Exclusion criteria during the study were as follows: nonadherence to the treatment, presence of any adverse effects resulting in patients' intolerance or complications, and unwilling or unable to follow the study protocol.

Sample size and randomization

A sample size of 65 patients in each group was calculated to detect 0.8 ng/mL mean difference serum level of 25(OH)D between two groups, while considering $\alpha = 5\%$, a power of 80%, and 20% dropout.

Considering the 25(OH)D level <30 ng/mL, of 395 subjects who were screened, 205 subjects had vitamin D deficiency, but only 130 subjects met the inclusion/exclusion criteria. Eligible patients based on inclusion and exclusion criteria, with moderate to severe vitamin D deficiency, were assigned into two different regimen treatment groups by block randomization method: one group received 50,000 IU oral softgel cholecalciferol (50,000 IU vitamin D3, Zahravi, Tabriz, Iran) weekly for eight weeks and the other group received 4,000 IU oral softgel cholecalciferol daily for 14 weeks (two units of softgel 2,000 IU vitamin D_3, Zahravi) to obtain the same cumulative dose. No placebo drug was used in this study. Patients were instructed to consume vitamin D_3 supplements each morning. Adherence to study medication was assessed by collecting all used and unused medications at the end of the treatment period. To assure adequate calcium intake, during the entire study period, 400 mg elemental calcium (as 1000 mg calcium carbonate salt) was administrated daily to the study patients in both groups. Participants were instructed to take the calcium supplements in two divided doses with meals. Moreover, subjects were allowed to continue their routine (daily diet and lifestyle).

At the baseline, required demographic characteristics of the study patients (age, sex, height and weight, BMI, average time of daily sunlight exposure, mean amounts of vitamin D[31] and calcium was taken from foods according to previous similar study,[32] comorbidities, and concomitant medications) were recorded. At the baseline and at the end of the study, blood samples were taken to measure 25(OH)D level using human enzyme-linked immunosorbent assay (ELISA) kit (Biorexfars, Tehran, Iran). Also, the serum level of calcium was measured in all recruited patients and was corrected according to the serum level of albumin.

Data analysis

The obtained data were analyzed by the Statistical Package for the Social Sciences (SPSS) software (version 16.0, SPSS, Chicago, Illinois). On the basis of the qualitative and quantitative nature of variables, the chi-square test and independent *t* test were used to statistically analyze the qualitative and quantitative variables. *P*-value <0.05 was considered as the significance level.

Results

The flow diagram of participants is shown in Figure 1. Overall, of 395 participants who were screened for vitamin D deficiency, 205 subjects (51.89%) had hypovitaminosis D (serum level of 25(OH)D <30 ng/mL) and 190 subjects (48.11%) had serum level of 25(OH)D >30 ng/mL, which was considered as vitamin D sufficiency. Baseline demographic characteristics of screened subjects are shown in Table 1. No significant differences were observed between subjects with or without vitamin D deficiency regarding baseline demographic characteristics such as mean dietary intake of vitamin D, mean sun exposure, and BMI. The mean age of the subjects with and without vitamin D deficiency was 40.52 ± 15.53 and 36.06 ± 15.46 years, respectively, which showed that the average age of subjects with vitamin D deficiency was significantly higher as compared to that of subjects without vitamin D deficiency. Vitamin D deficiency was also more prevalent in women compared to that in men. Higher percentage of subjects without vitamin D deficiency had a history of vitamin D supplementation during one year before the study.

Of 130 subjects with moderate to severe hypovitaminosis D, who were allocated into study groups, 55 subjects in 4,000 IU oral vitamin D_3 daily group and 52 subjects in 50,000 IU oral vitamin D_3 weekly group completed the entire study. No significant differences were observed between the two groups regarding baseline demographic characteristics [Table 2]. Approximately 69.16% of the study patients were female, and the mean age of subjects in daily and weekly groups was 39.58 ± 14.04 and 41.31 ± 14.35 years, respectively. Participants in both groups were comparable regarding the comorbidity and concomitant medication.

As shown in Table 3, the mean serum level of 25(OH)D at baseline was 10.68 ± 5.16 IU and 12.25 ± 4.83 ng/mL in daily and weekly regimen groups, respectively, which was statistically comparable. Although at the end of the study period, the serum level of 25(OH)D increased significantly in both groups (40.25 ± 9.33 and 36.92 ± 13.19 ng/mL in daily and weekly regimens, respectively), the obtained results showed that daily regimen was significantly more effective than weekly regimen in increasing the serum level of 25(OH) D ($P = 0.04$). Moreover, the mean difference of serum level of 25(OH)D at the baseline and at the end of the treatment in the daily regimen group was significantly higher compared to the weekly regimen group (28.45 ± 8.32 vs. 22.53 ± 688 ng/mL, $P \leq 0.001$). The serum level of 25(OH)D in 46 (83.6%) subjects in the daily regimen group and in 34 (65.4%) subjects in the weekly regimen group reached above 30 ng/mL, which showed that a higher percentage of the subjects in the daily regimen group can achieve sufficient serum level of 25(OH) D compared to the weekly regimen group. Furthermore, no significant differences were observed between the two groups regarding the serum level of corrected calcium at the baseline and at the end of the study [Table 3].

Discussion

According to the results of this study, the prevalence of vitamin D deficiency was relatively high (51.9%) in the study population. The prevalence of hypovitaminosis D was higher in female, subjects with higher age, and subjects with a lack of history of supplementation with vitamin D during one year before the study. Furthermore, the results showed that although both daily and weekly vitamin D3 regimens were effective in increasing the serum level of 25(OH)D, the daily vitamin D3 regimen in similar cumulative doses was more effective than the weekly vitamin D3 regimen in increasing the serum level of 25(OH)D. Further, a higher percentage of the subjects in the daily regimen group can reach sufficient serum level of 25(OH)D in comparison with the weekly regimen group (serum level above 30 ng/mL). These results may be attributed to the better bioavailability of daily regimen and establishment of the steadier serum level of 25(OH)D.

The prevalence of vitamin D deficiency is different worldwide, and it depends on several factors such as the definition of serum level of 25(OH)D, which is considered as vitamin D deficiency, the region and season of the year when the study subjects were evaluated, and the characteristics of the study population.[29] The prevalence of vitamin D deficiency in south and southeast Asian countries such as Pakistan was reported up to 98% that can be attributed to the skin color, special clothing, and low sunlight exposure of the people in this region.[33-36] In comparison, the prevalence of vitamin D deficiency in countries such as Vietnam and Japan was relatively low, which maybe due to people's dietary habits and sufficient intake of food rich with vitamin D such as marine foods and natural supplements of cod liver oil.[37,38]

It seems demographic factors such as age, sex, skin color, and BMI can affect the prevalence of vitamin D deficiency.[16,39] Results of our study, which were consistent with the previous

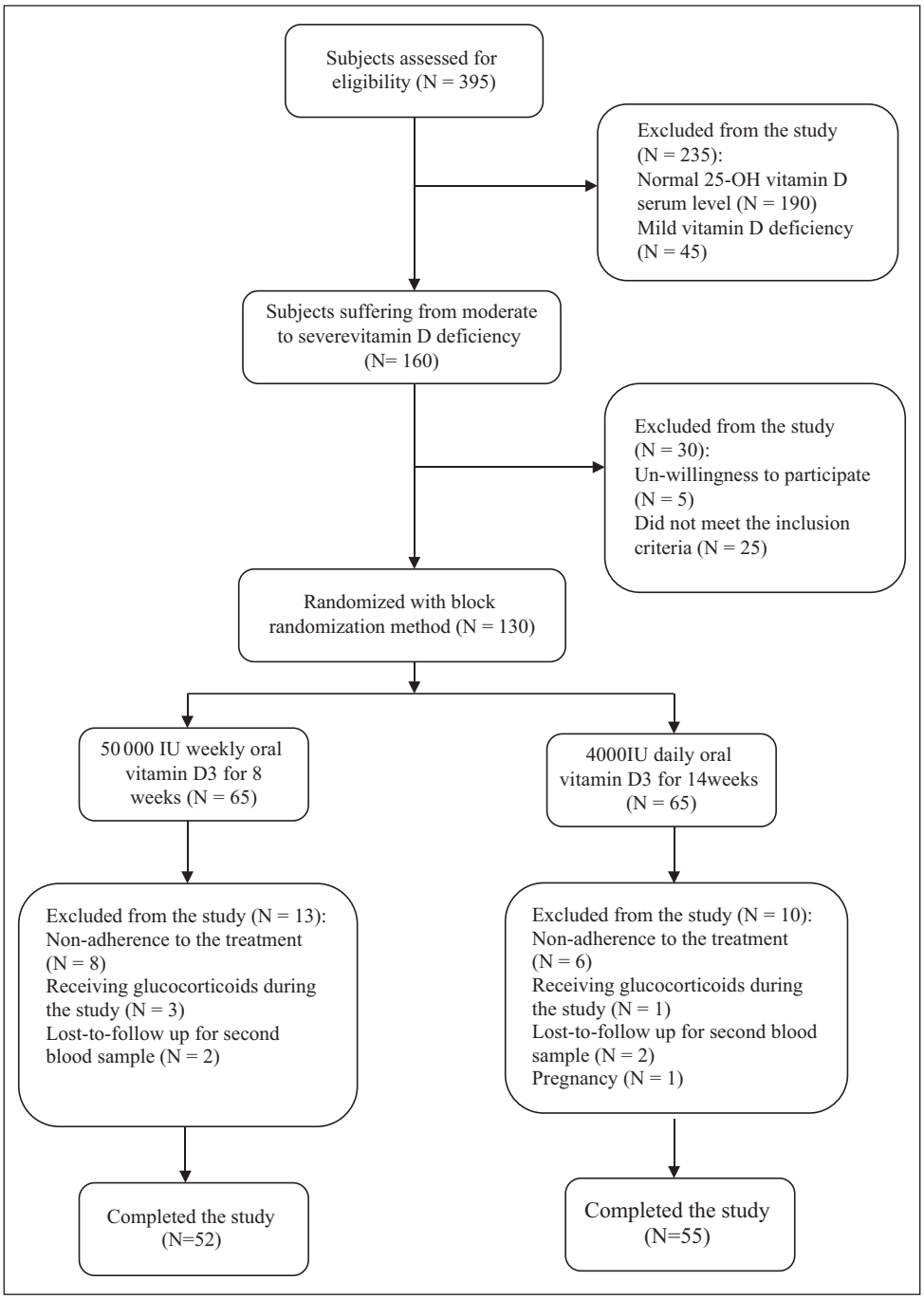

Figure 1: Flow diagram of the study

studies, showed that with increasing age, the prevalence of vitamin D deficiency increased, which can be attributed to comorbidities and declining cutaneous synthesis of vitamin D with increasing age.[40,41] Regarding the higher prevalence of vitamin D deficiency in women, our results were also consistent with previous reports.[42,43]

Results of this study, similar to previous studies, showed that dietary and supplementary intake of vitamin D can reduce the prevalence of vitamin D deficiency.[40] Supporting the importance of vitamin D supplementation in the prevention of vitamin D deficiency, the prevalence of hypovitaminosis D was found to be relatively low in the residents of high-latitude countries in northern Europe, despite insufficient exposure to sunlight, which could be due to the routine use of vitamin D supplement and fortification foods with vitamin D by the residents of these countries. Therefore, the fortification of foods with vitamin D and consumption of vitamin D supplements is one of the effective strategies for the prevention of vitamin D deficiency, especially in people at higher risk for hypovitaminosis D.[4,40,44]

A varying prevalence of hypovitaminosis D was reported in Iran. Hashemipour *et al.*[45] reported that the prevalence of vitamin D deficiency was approximately 81.3% in a city such

Table 1: Demographic characteristics of the subjects with/without vitamin D deficiency

Variable	Subjects with vitamin D deficiency	Subjects without vitamin D deficiency	*P* value
Sex (*N*; male/female)	66/139	88/102	0.004
Age (years; mean ± SD)	40.52 ± 15.53	36.06 ± 15.46	0.004
BMI (kg/m^2; mean ± SD)	24.61 ± 3.17	24.24 ± 3.18	0.252
Mean dietary intake of vitamin D (IU; mean ± SD)	154.39 ± 77.64	153.55 ± 79.62	0.916
Mean sun exposure (minutes; mean ± SD)	22.59 ± 13.27	23.03 ± 14.06	0.74
History of vitamin D supplement consumption (N; yes/no)	19/186	103/87	<0.001

BMI = body mass index, SD = standard deviation

Table 2: Demographic characteristics of the study groups

Variable	4000 IU daily group (*N* = 55)	50000 IU weekly group (*N* = 52)	*P* value
Sex (*N*; male/female)	16/39	17/35	0.68
Age (years; mean ± SD)	39.58 ± 14.04	41.31 ± 14.35	0.53
BMI (kg/m^2; mean ± SD)	24.53 ± 3.09	24.05 ± 3.72	0.47
Mean dietary intake of vitamin D (IU; mean ± SD)	148.64 ± 90.06	156.73 ± 72.10	0.61
Mean sun exposure (minutes; mean ± SD)	23.45 ± 14.23	20.96 ± 12.00	0.33
Mean dietary calcium intake (mg; mean ± SD)	871.82 ± 65.09	880.77 ± 7.26	0.48
History of vitamin D supplement consumption (*N*; yes/no)	2/53	2/50	0.99

BMI = body mass index, SD = standard deviation

Table 3: 25-Hydroxyvitamin D and corrected calcium serum levels of the study groups (as mean ± standard deviation)

Variable	4000 IU daily group (*N* = 55)	50000 IU weekly group (*N* = 52)	*P* value
25-OH-vitamin D serum level at baseline	10.68 ± 5.16	12.25 ± 4.83	0.1
25-OH-vitamin D serum level at the end of treatment	40.25 ± 9.33	36.92 ± 13.19	0.001
P value	<0.001	<0.001	
Mean change of 25-OH-vitamin D serum level from baseline to end of treatment	28.45 ± 8.32	22.53 ± 6.88	≤0.001
25-OH-vitamin D serum level above 30 ng/mL; *N* (%)	46 (83.6%)	34 (65.4%)	0.04
Corrected calcium serum level at baseline	9.13 ± 0.52	9.23 ± 0.57	0.32
Corrected calcium serum level at the end of study	9.12 ± 0.55	9.21 ± 0.57	0.37
P value	0.65	0.45	

as Tehran and was higher in women compared with men, which was consistent with our results. In contrast, they found that vitamin D deficiency was higher in younger women than the elderly, which can be explained by the increased usage of vitamin D supplement for relieving musculoskeletal pain in the elderly and the sedentary lifestyles, especially in young people in recent years in Iran. Air pollution and different lifestyles in the residents of metropolitan cities such as Tehran in comparison to those in the small city of our study are other factors that can contribute to the higher prevalence of vitamin D deficiency in such cities. Also, considering the increased awareness of people in recent years, regarding the importance of vitamin D in physical and mental health status, the consumption of vitamin D as a supplement has been increased as well.

Given the beneficial effects of vitamin D in maintaining the physical and mental health and the multiple adverse consequences of vitamin D deficiency, it seems important to find an effective regimen for vitamin D replacement therapy. Multiple dosing regimens are used in the treatment of vitamin D deficiency. In general, weekly 50,000 IU of vitamin D3 for eight weeks is used as regimen of vitamin D replacement in subjects with hypovitaminosis D due to better adherence to the treatment by patients.[8] Research studies, investigating the efficacy of different dosing regimens of vitamin D supplementation in the treatment of hypovitaminosis D, have shown inconsistent findings. In a study conducted by Chel *et al.*,[28] the effectiveness of 600 IU daily, 4,200 IU weekly, and 18,000 IU monthly of oral vitamin D3 regimens was compared in the elderly patients living in nursing homes. Consistent with the results of our study, although all three regimens were effective in increasing the serum level of 25(OH)D, the daily vitamin D3 regimen was more effective than weekly and monthly regimens.[28] Other relevant studies reported conflicting results in this regard. For example, Ish-Shalom *et al.*[27] performed a study in the elderly women with hip fractures. They concluded that three regimens of vitamin D (1,500 IU daily, 10,500 IU weekly, and 45,000 IU monthly) were comparable in the treatment of hypovitaminosis D.[27] These mixed results may be related to the higher average age of the study subjects in the mentioned study compared to our study subjects

as well as using a crystalline form of vitamin D3 in ethanol that enhances the bioavailability of vitamin D3. Also, a recent study conducted by De Niet *et al.*[46] in Belgium revealed that daily (2,000 IU) and monthly (50,000 IU) administration of vitamin D_3 in equivalent cumulative dosage are similarly effective in the normalization of serum levels of 25(OH)D in the subjects with vitamin D deficiency, and even the monthly supplementation regimen produced a more rapid increase in the serum levels of 25(OH)D compared to daily supplementation regimen. These discrepancies can be partially justified by the differences in the vitamin D dosage, frequency of administration, and duration of the treatment in a study by De Niet *et al.*[46] compared to those in our study. In addition, in a developed country, such as Belgium, a significant amount of daily requirement of vitamin D comes from fortified diet, whereas a very low fortified diet with vitamin D is available to the residents of the developing countries such as Iran, and supplementation remains the only source of adequate vitamin D intake.

Results of a study by Saadi *et al.*[47] showed that although supplementation with 2,000 IU vitamin D2 daily and 60,000 IU vitamin D2 monthly in lactating and nulliparous women with hypovitaminosis D can increase the serum level of 25(OH) D, D2 form of vitamin D was not as effective as vitamin D3 supplementation in the treatment of hypovitaminosis D. Therefore, higher doses of vitamin D2 supplement may be required for the treatment of hypovitaminosis D. The study by Saadi *et al.*[47] also showed that the daily regimen was more effective than the monthly regimen in increasing the serum level of 25(OH)D.

In another study conducted in the elderly women, although annual 500,000 IU oral vitamin D3 in comparison with placebo increased the serum level of 25(OH)D, the high dosing regimen of vitamin D3 was accompanied with the higher risk of fractures and falls in the study population.[41] Therefore, in addition to the effectiveness of the chosen regimen in increasing the serum level of 25(OH)D, the safety of the vitamin D replacement regimen is another important factor that should be considered in the treatment of hypovitaminosis D. Therefore, it is recommended to evaluate the effectiveness, as well as the safety of different regimens of vitamin D in the treatment of hypovitaminosis D in future studies.

This study had several limitations; it was conducted in the residents of a limited area of Iran with special weather, so we cannot generalize our results to the residents of other regions of Iran. However, even in a limited population of our study, different vitamin D regimens showed different effects in increasing the serum level of 25(OH)D. Also, owing to the financial limitations, the serum level of parathyroid hormone, another important hormone in the hemostasis of bone, which is affected by vitamin D, was not measured in this study, which should be considered in future studies. Further, only two samples were taken from each patient (at the baseline and at the end of the treatment). Therefore, the quality of the data does not allow a deeper inspection and understanding of the biochemical changes of serum level of 25(OH)D in the study groups. In addition, owing to short duration of the study, evaluating the influence of the regimens on the clinical outcomes was not possible.

Conclusion

In conclusion, although the weekly regimen of vitamin D due to the lower frequency of drug intake may possess higher acceptability among the patients, daily regimen of vitamin D3 in similar cumulative doses was more effective in increasing the serum level of 25(OH)D probably because of its better bioavailability. So, according to the available evidence, a fixed-dosing regimen cannot be effective in all population and it is necessary to evaluate the effectiveness of treatment via measuring serum level of 25(OH)D, after treating hypovitaminosis D.

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Conflicts of interest

There are no conflicts of interest.

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