INTRODUCTION
Bone, skeletal muscle, brain, heart, prostate, colon, breast tissues and immune cells have Vitamin D receptors which are sensitive to the active form, calcitriol, also known as 1,25 dihydroxyvitamin D or $1,25(OH)_2D$.
Apart from its well-known effects on bone turnover, clinical studies suggest that extra-skeletal effects of Vitamin D are substantial in severe deficiency of Vitamin D. Age-related alterations may lead to decreased formation of the active form of Vitamin D. Vitamin D deficiency is commonly seen in nursing home residents and has to do with a reduction in mobility, time spent outdoors with sun exposure, intrinsic skin response to ultraviolet radiation, inadequate dietary Vitamin D intake, impaired absorption, liver/kidney dysfunction, multiple comorbidities, and possibly polypharmacy.

ABSTRACT
Objective: To investigate the effectiveness of daily (800 IU), weekly-moderate (5600 IU) and weekly-high (8000 IU) supplementation of Vitamin D in nursing home residents.
Study Design: A descriptive study.
Place and Duration of Study: Nursing Home, MEVA, Istanbul, Turkey, from July 2016 to July 2017.
Methodology: Nursing home residents were divided into 3 groups for supplementation of Vitamin D: Daily Dose Group (DDG), Weekly Dose Group-moderate (WDG-moderate) and Weekly Dose Group-high (WDG-high). Blood and physical performance tests were done initially to obtain a baseline value and the tests were repeated at 13th and 26th weeks of supplementation. Statistical analysis was conducted only on patients who were able to complete the 6-month-long study.
Results: WDG-moderate (5600 IU/week) supplementation is found to be the most effective intervention in our study [25 (OH) D from 23.50 ±12.67 ng/mL to 37.38 ±14.42 ng/mL]. In WDG-moderate, the resulting Vitamin D level was found to reach near-optimum therapeutic levels. Only a limited increase was observed in 25 (OH) D level of DDG and WDG-high at the end of 26 weeks.
Conclusion: Weekly (5600 IU/week) moderate supplementation of Vitamin D could be more beneficial than weekly (8000/week) high supplementation among nursing home residents. Multi-drug use among nursing home residents may hinder the therapeutic efficiency of Vitamin D administration. Physical performance tests may fail to demonstrate increased performance in mobility after Vitamin D administration in nursing home residents.


High versus Moderate Dosage of Daily and Weekly Administration of Vitamin D Supplements in the Form of Oil Drop in Nursing Home Residents
Rezzan Mol1, Ahmet Dogukan Kansu2, Tamer Cebe2, Sadik Yildiz1, Vildan Kandemir Butun1, Bahadir Simsek2 and Ufuk Cakatay3

ORIGINAL ARTICLE

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Bone, skeletal muscle, brain, heart, prostate, colon, breast tissues and immune cells have Vitamin D receptors which are sensitive to the active form, calcitriol, also known as 1,25 dihydroxyvitamin D or 1,25 (OH)$_2$D.\textsuperscript{1} Apart from its well-known effects on bone turnover, clinical studies suggest that extra-skeletal effects of Vitamin D are substantial in severe deficiency of Vitamin D. Age-related alterations may lead to decreased formation of the active form of Vitamin D.\textsuperscript{2} Less than 20 ng/mL (50 nmol/L) of 25-hydroxyvitamin D is defined as Vitamin D deficiency.

Vitamin D deficiency is commonly seen in nursing home residents and has to do with a reduction in mobility, time spent outdoors with sun exposure, intrinsic skin response to ultraviolet radiation, inadequate dietary Vitamin D intake, impaired absorption, liver/kidney dysfunction, multiple comorbidities, and possibly polypharmacy.\textsuperscript{3,4} The prevalence of Vitamin D deficiency in nursing home residents was found to be extremely high (from 79 to 98%).\textsuperscript{5,6} In nursing homes, Vitamin D supplementation is increasingly considered to be a standard of care and, therefore, part of a good medical practice for elderly care.\textsuperscript{3} There is considerable discussion about optimum serum concentrations of 25-hydroxyvitamin D. The prevalence of 25-hydroxyvitamin D deficiency affects more than 25% of community-dwelling elderly and the prevalence of deficiency is almost doubled among nursing home residents.\textsuperscript{7} It was reported that more than half of physicians systematically prescribe Vitamin D in Belgium, because they believe nursing home residents are mostly deficient in Vitamin D.\textsuperscript{8} Vitamin D supplementation may contribute to improved health status, musculoskeletal performance and reduce the risk of falls by improving strength, balance and elderly death in nursing homes.\textsuperscript{9}

The purpose of the current study was primarily to evaluate the effectiveness of daily, weekly moderate and weekly high administration of emulsified oil drop Vitamin D supplements in nursing home residents.
METHODOLOGY

This descriptive study was conducted from July 2016 to July 2017 in Nursing Home, MEVA, Istanbul, Turkey in collaboration with Istanbul University, Cerrahpasa Faculty of Medicine.

Nursing Home residents were included while those who met at least one of the following conditions were excluded from the study: age <65 years, plasma 25 (OH) D >50 nmol/L, malignant disease, renal, hepatic, gastrointestinal disorders, endocrine disease associated with abnormal calcium metabolism that required therapy (Diabetes mellitus type 2 or hypothyroidism were permitted for inclusion); life expectancy of <6 months, creatinine clearance <30 mL/min, diagnosed with granulomatous disease, use of glucocorticoids, anticonvulsants, Vitamin D supplements or other medications known to affect calcium or bone metabolism in the previous 12 months or past hip fracture. Other daily medications were continued during the study. The study was reviewed and approved by Cerrahpasa Faculty of Medicine, Istanbul University Ethics Committee (File number: 18/07/2016-259249).

Table I: Overall distribution of subjects in various groups at different time lines.

<table>
<thead>
<tr>
<th>Randomisation</th>
<th>T=0, baseline</th>
<th>T=13 weeks</th>
<th>T=26 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Daily Dose Group (DDG)</td>
<td>n=12</td>
<td>n=11 (1 death)</td>
</tr>
<tr>
<td></td>
<td>800 IU/day n=12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group II</td>
<td>Weekly Dose Group-moderate (WDG-moderate)</td>
<td>n=11 (1 death)</td>
<td>n=8 (3 deaths)</td>
</tr>
<tr>
<td></td>
<td>5600 IU/week n=12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group III</td>
<td>Weekly Dose Group-high (WDG-high)</td>
<td>n=11 (1 death)</td>
<td>n=10 (1 death)</td>
</tr>
<tr>
<td></td>
<td>8000 IU/week n=12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The sample size calculation was based on a previous study that enrolled 30 patients and evaluated mean changes in serum Vitamin D in elderly patients with Vitamin D administration. Participants were divided into homogenous 3 groups (Table I) using the minimisation method based on body weight, gender, the ability to walk and basal Vitamin D status. The safe Vitamin D dosages and administration intervals were adjusted on the basis of aforementioned reports which recommend the administration of relatively moderate and moderately-high dosages of Vitamin D to improve general health status of elderly home residents.

Group I was labelled daily dose group (DDG-moderate) and given (800 IU/day=5600 IU/week=24000 IU/month= 288000 IU/year. Group II was labelled weekly dose group-moderate (WDG-moderate) and given 5600 IU/week=24000 IU/month=288000 IU/year. Group III was labelled weekly dose group-high (WDG-high) and given 8000 IU/week=32000 IU/month= 384000 IU/year. 25-hydroxyvitamin D was given to the elderly individuals as drops which were a fluid mixture composed of 25-hydroxyvitamin D3 and butylhydroxyanisole in star anise oil (Dvit-3 Oral Drop, Deva, Istanbul, Turkey). To minimize dosage errors, the nursing staff was informed about the correct method of delivery. Compliance with the ingestion of drops was 100% in all participants and drops were administered by a tea spoon with fruit juice, or in a small quantity of tea or water.

Dietary intake of Vitamin D was assessed using a food frequency questionnaire (FFQ) for 4-day food record in Nursing Home residents. The FFQ was filled out by residents and average daily nutritional intake of Vitamin D was calculated. Functional ambulation classification (FAC) was used as an assessment of the mobility. Activities of daily living were assessed using the Barthel Index (BI). Physical performance tests namely; handgrip strength (HGS), two minute walking test (2MWT) and the timed up and go tests (TUG) were done prior to supplementation and re-done 13th and 26th weeks of supplementation. HGS value was assessed twice with an HGS dynamometer (Saehan Corporation, South Korea) for both hands on each occasion. The highest value (kg) was used for statistical analysis. 2MWT was assessed in a walking course of 6x4 m and was reported as walking distance (m) to test balance and exercise capacity. TUG test was performed in an armless chair with a standardised walking distance and average time to test mobility. All physical performance tests were performed and assessed by a physiotherapist who was blinded to the Vitamin D supplementation groups.

Blood samples were collected for the analysis of various parameters such as 25-hydroxyvitamin D, parathyroid hormone (PTH), calcium, phosphate, total protein, albumin and creatinine. Serum 25-hydroxyvitamin D level was determined by solid phase enzyme linked Immunosorbent assay (Epitope Diagnostics, San Diego, CA, USA). The assay has 100% cross-reactivity with 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3. Serum calcium, phosphate, total protein, albumin, creatinine levels were analysed on CRONY Saturno 300 discrete clinical chemistry autoanalyser (Rome, Italy). PTH level was also measured on Immulite 2000 XPi immunoassay system (IMMULITE® Siemens Healthcare Diagnostics, Erlangen, Germany). The medical laboratory where the tests were done is certified by TURKAK (Turkish Accreditation Agency) and participates in external quality assessment schemes organised by the Reference Institute for Bioanalytics (RfB). Total calcium concentrations were corrected for albumin according to the following equation; Ca corr = total calcium-(0.025 x albumin) + 1, expressed in mmol/L.

The statistical analysis was carried out with SPSS 24.0. Data from only those patients who were able to complete 26-week-long study were used in statistical analysis.

Vitamin D level of patients was tested for normality with the following equation; Ca corr = total calcium-(0.025 x albumin) + 1, expressed in mmol/L.

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Vitamin D level of patients was tested for normality with the following equation; Ca corr = total calcium-(0.025 x albumin) + 1, expressed in mmol/L.
Shapiro-Wilk test, histogram and Q-Q plot, and the data were found to be near-normally distributed. Following this, one-way ANOVA with Bonferroni test was performed. Significance level was set to p<0.05. Data are presented as mean ± SD with 95% confidence interval. For the non-normally distributed parameters (PTH and creatinine), median value (IQR) is used to present the data.

RESULTS

The present research was carried out with 36 Nursing home residents (14 males, 22 females; 81.65 ±7.44 years). During one year after admission (n=165), the mortality rate of the residents of MEVA Nursing Home (Istanbul Turkey) was 35% (n=58). The primary cause of death was determined to be cardiac/pulmonary 62% (n=36), malignancy 35% (n=20), 3% (n=2) amyotrophic lateral sclerosis. During the study, nutritional intake of Vitamin D of Nursing Home residents was found to be similar throughout all the groups, around 55 IU/day; on average.

As shown in Table II, in WDG-moderate and to some extent in DDG, Vitamin D level was found to increase. In WDG-high, patients could not tolerate the amount of supplementation and gastrointestinal symptoms were observed. Lab results are given in Table II.

Vitamin D level in DDG at baseline was T₀=21.55 ±8.28 ng/mL (95% confidence interval from 15.98 to 27.11). T₂₆=26.73 ±9.72 ng/mL (95% confidence interval from 20.19 to 33.26), (T₀ vs T₂₆ DDG, p=1.000).

As for WDG-moderate, T₀= 23.50 ±12.67 ng/mL (%95 confidence interval from 12.91 to 34.09). T₂₆=37.38 ±14.42 ng/mL (%95 confidence interval from 25.32 to 49.43), (T₀ vs T₂₆ WDG-moderate, p=0.335).

WDG-high intervention did not increase serum 25(OH)D level appreciably, only from T₀= 27.70 ±6.60 ng/mL to T₂₆= 29.00 ±7.00 ng/mL. Physical tests including HGS, TUG, 2MWT did not result in increased performance following Vitamin D supplementation in any group.

DISCUSSION

Vitamin D administration types, periods and methods differ from one study to another. The optimum dose of Vitamin D administration is still debated.14-16

Vitamin D deficiency may play a role in oncogenesis, cardiovascular disorders such as stroke, myocardial infarction and hypertension.17-19 The Endocrine Society recommends all Vitamin D-deficient adults be treated with 50,000 IU of Vitamin D2 or Vitamin D3 once a week for 8 weeks or its equivalent of 6000 IU of Vitamin D2 or Vitamin D3 daily to achieve a serum 25 (OH) D above 30 ng/mL, followed by maintenance therapy of 1500-2000 IU/d.7 However, there is a lack of consensus regarding the dosing schedule to achieve this level and also the route.20 It is also recommended that 300000-500000 IU/year of Vitamin D be administrated to elderly in nursing homes, to improve general health and reduce the risk of falls by improving strength and balance.15,16 Because of ethical reasons, due to previously shown very serious side effects such as falling and hip fractures of high supplementation of Vitamin D, Nursing Home resident groups were administrated much lower dosages than what Endocrine Society recommends, a decision quite similar with the literature cited above.

Polypharmacy is a newly put forth risk factor which came under spotlight in recent years.4 In elderly patients who were not included in Vitamin D supplementation programs, inverse relationship between serum 25 (OH) D level and polypharmacy was recently reported.4 It was
found that the elderly who are under polypharmacy risk (>5 medication) or severe polypharmacy risk (>10 medication) and who uses especially: oral antidiabetics, Vitamin K antagonists, cardiac glycosides, potassium sparing diuretics, ACE inhibitors, selective serotonin reuptake inhibitors are under the risk of Vitamin D deficiency. In this study, not only the patients were quite similarly distributed in terms of the drug types they use; but also in all 3 groups, polypharmacy and severe polypharmacy incidence was very similar, barring our study from possible confounding effects of polypharmacy.

Elderly patients who received weekly moderate supplementation (5600 IU/week) showed better serum Vitamin D profile than DDG and WDG-high. It should be noted that Vitamin D could be absorbed and better tolerated in DDG, WDG-moderate; but weekly high dose supplements might not have been fully absorbed due to its diarrhea inducing effects seen in some of these patients. The present results are consistent with those that showed an association between hypovitaminosis D and frailty in Nursing Home residents and elderly. Although the current study design does not show a causation between Vitamin D deficiency and frailty in elderly, a coexistence was observed between impaired Vitamin D status and increased frailty. Possibly, Vitamin D supplementation did not result in improved physical performance tests due to the limited increase in circulating 25 (OH) D level. In DDG, WDG-moderate and WDG-high groups, 65% of patients had polypharmacy and around 35% had severe polypharmacy. Considering that the exclusion criteria were quite strict and neither kidney nor liver disease patients were enrolled, the resistance observed hampering a palpable and possibly therapeutic increase in Vitamin D level be partly due to polypharmacy. Considering the high mortality rate and newly suggested extra-skeletal effects of Vitamin D, increasing serum Vitamin D level to optimum values may ensure a decreased mortality in this frail group.

The apparent limitation of the current study, even though more patients were enrolled than other groups, could be the number of participants. Based on previously published papers on Vitamin D, the sample size is sufficient, as shown by mean values and confidence intervals. In this frail elderly group, it is not possible to ensure long-term follow-ups due to high mortality rate as exemplified in this study where 7 out of 36 patients died in just 6 months. Most family caregivers in Turkey prefer caring for their elderly parents with chronic disease and/or age-related disorders at caregivers' home. Despite traditional culture within Turkish families, in some cases, hospitalization of the elderly in nursing home is inevitable, and this negatively affects the elderly individual and his/her siblings.

This study has several noteworthy strengths. It contributes to the literature as novel data showing the effectiveness of WDG-moderate (5600 IU/week) of Vitamin D supplements in the form of emulsified oil drop in patients with polypharmacy and cardiovascular morbidities. Healthcare providers for nursing home residents should be aware of this possibly polypharmacy related Vitamin D deficiency and be aware of the effectiveness of moderate weekly supplementation to exclude newly suggested extra-skeletal effects of Vitamin D deficiency. Further studies, preferably multicenter studies of nursing home residents with large numbers of participants are warranted to better understand the proposed polypharmacy related effects on Vitamin D depletion and involvement of Vitamin D in a variety of disorders.

CONCLUSION
WDG-moderate supplementation of 25-hydroxyvitamin D3 (5600 IU/week) were found to increase 25 (OH) D level, more than WDG-high (8000 IU/day) which was associated with adverse gastrointestinal symptoms. The resistance of 25 (OH) D level against rising may be due to newly suggested polypharmacy effect.

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