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Efficacy of a Standardized Oral Vitamin D Dosing Regimen in Nursing Home Residents

Marlous Toren-Wielema¹ · Ruth Veenhuizen² · Jan Willem Kappelle³ · Nic Veeger⁴ · Eric van Roon^{1,5}

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Abstract

Background The prevalence of vitamin D deficiency in nursing home residents ranges from 79% to 98%.

Objectives The aim of this cross-sectional observational study in somatic and psychogeriatric nursing home residents was to determine the efficacy of a standardized oral vitamin D dosing regimen (VDDR) consisting of a loading dose (LD) of cholecalciferol 200,000 IU followed by a maintenance dose (MD) of 100,000 IU every 13 weeks in obtaining and maintaining an adequate and safe vitamin D trough level (VDTL), defined as 75–220 nmol/L (reference range).

Methods Blood samples of nursing home residents who had received the LD followed by at least one MD were analyzed for VDTL, calcium, parathyroid hormone, and creatinine. Data on age, sex, race, body weight and height, co-morbidity, co-medication, number of MDs, calcium supplementation, smoking, and use of alcohol were obtained from patient charts. The primary outcome for the efficacy of the VDDR was the percentage of nursing home residents with a VDTL 75–220 nmol/L, with a target percentage of 85% for the dosing regimen to be considered efficacious.

Results In 91 (58%; 95% confidence interval [CI] 50–66) of 156 included nursing home residents, a VDTL within the reference range was measured (mean [standard deviation] 81 [28] nmol/L, range 13–150 nmol/L). The only variable that was identified as a significant risk indicator for obtaining a VDTL ≥ 75 nmol/L was the number of MDs being four or more (≥ 4 vs. < 4 ; odds ratio 2.7; 95% CI 1.4–5.3).

Conclusion This standardized VDDR was not efficacious in obtaining and maintaining an adequate VDTL in this nursing home resident population.

Clinical trials registration number NTR6029 (The Netherlands National Trial Register).

Key Points

In the nursing home resident population, a cholecalciferol loading dose (LD) is needed to raise the 25-hydroxy-vitamin D concentration to ≥ 75 nmol/L, after which a maintenance dose (MD) is required to maintain adequate levels.

However, a standardized oral cholecalciferol dosing regimen consisting of an LD of 200,000 IU followed by an MD of 100,000 IU every 13 weeks was not efficacious in obtaining and maintaining an adequate vitamin D trough level.

The findings in this study stress the need for research on effective correction of deficient vitamin D levels in nursing home residents.

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1 Background

Vitamin D plays an integral role in calcium and phosphate homeostasis, with the active metabolite 1,25-dihydroxyvitamin D promoting mineralization of the skeleton by maintaining adequate serum calcium levels through facilitation of intestinal absorption and stimulation of mobilization from bone [1]. Serum 25-hydroxyvitamin D, obtained by hepatic hydroxylation of vitamin D₃, represents the predominant circulating vitamin D metabolite and is considered the best indicator of vitamin D status, reflecting dietary intake as well as cutaneous synthesis through sunlight exposure and production from endogenous processes. 25-Hydroxyvitamin D levels are inversely correlated with serum parathyroid hormone (PTH), a key calcium-regulating polypeptide that indirectly promotes bone resorption through activation of osteoblasts. Osteoblasts stimulate the differentiation of osteoclasts, which cause the mineralized collagen matrix in bone to dissolve and calcium to be released into the blood [1].

While the target serum 25-hydroxyvitamin D concentration for optimal skeletal health is debated, a threshold of 75 nmol/L has been associated with increased efficiency of intestinal calcium absorption as well as normalization of PTH levels [2–4]. These biochemical effects were found to be consistent with the threshold for prevention of non-vertebral and hip fractures in a meta-analysis of double-blind randomized controlled trials among older individuals (age ≥ 65 years), as optimal fracture prevention occurred with achieved mean 25-hydroxyvitamin D levels of at least 75 nmol/L [5]. Based on these biochemical and clinical findings, guidelines by the International Osteoporosis Foundation (IOF) and the Endocrine Society (ES) advocate a target serum 25-hydroxyvitamin D level of 75 nmol/L at an older age [6, 7]. However, evidence discussed by the Institute of Medicine (IOM) suggests a serum 25-hydroxyvitamin D level > 50 nmol/L as being sufficient, as levels > 75 nmol/L were found not to be consistently associated with increased benefit [8]. Although there is no consensus regarding the optimal serum vitamin D level, vitamin D deficiency is defined as a 25-hydroxyvitamin D level less than 50 nmol/L and levels < 25 nmol/L indicate severe vitamin D deficiency according to the majority of published guidelines [8, 9]. The first measurable consequences of vitamin D toxicity are hypercalciuria and hypercalcemia, which have been observed at 25-hydroxyvitamin D levels above 220 nmol/L [10].

In nursing home residents, a low vitamin D status has been associated with a variety of musculoskeletal consequences (muscle weakness, osteomalacia, increased body sway, falls, and fractures) as well as fatigue and prolonged

length of stay in case of hospitalization [5, 11]. With the prevalence of vitamin D deficiency among nursing home residents ranging from 79% to as high as 98% [12, 13], it is essential to provide this population with adequate supplementation in order to restore vitamin D status. The most common form of vitamin D supplementation and the only available form of vitamin D in The Netherlands is vitamin D₃ (cholecalciferol). However, evidence-based guidelines for effective correction of deficient vitamin D levels with cholecalciferol in the nursing home population are lacking and daily supplementation of 800 IU failed to raise serum 25-hydroxyvitamin D levels to > 75 nmol/L in the majority of nursing home residents [14].

In 2010, a standardized oral vitamin D dosing regimen (VDDR) was introduced in the nursing homes of the Noorderbreedte Care Group. The purpose of this regimen was to achieve and maintain an adequate and safe vitamin D trough level (VDTL; defined as a serum 25-hydroxyvitamin D concentration 75–220 nmol/L), assuring a constant adequate vitamin D status without having to determine initial vitamin D status. The VDDR was ultimately standardized as a single oral loading dose (LD) of cholecalciferol 200,000 IU followed by a maintenance dose (MD) of 100,000 IU orally every 13 weeks. The aim of this cross-sectional observational study in somatic and psychogeriatric nursing home residents was to determine the efficacy of this standardized oral VDDR.

2 Methods

2.1 Study Design

This was a cross-sectional observational study in residents of 12 somatic and psychogeriatric nursing homes of the Noorderbreedte Care Group. All nursing homes are located in province of Fryslân, The Netherlands. The study is registered in The Netherlands National Trial Register (NTR6029). Cholecalciferol was dispensed by trained and skilled nursing home staff on fixed days and administered to the residents under direct observation. From January 2011 to December 2013, the doses were prepared from a 50,000 IU/mL oral solution by drawing up the required quantity in a syringe. From January 2014, ready-to-administer ampoules containing an oral solution of 100,000 IU/mL were used. Supplementation of other cholecalciferol preparations was stopped once patients were included in the VDDR.

Nursing home residents were eligible to participate in the study when they had received vitamin D supplementation according to the VDDR for at least 4 months (i.e., the LD followed by at least one MD). The doses were considered to be administered when there was a registration of the administration in the electronic medication

administration system. Previous vitamin D supplementation of cholecalciferol ≤ 800 IU/day was not considered to be an exclusion criterion as it was assumed that with these regimens serum 25-hydroxyvitamin D concentrations would not have been raised to ≥ 75 nmol/L. Subjects were selected to participate in the study by discretion of the elderly care physician.

In accordance with Dutch national law, formal ethical approval was not mandatory for this observational study, since the drawing of blood for measurement of laboratory parameters was standard of care for the Noorderbreedte nursing home residents who received the VDDR.

Subjects were excluded from the study when they had received additional cholecalciferol supplements (> 800 IU) outside the standardized VDDR or when a blood sample was not available from routine laboratory assessments.

2.2 Cholecalciferol Supplementation

The reference range for an adequate and safe vitamin D trough level was defined as 75–220 nmol/L. The study by van Groningen et al. [15] had demonstrated that a weight- and serum 25-hydroxyvitamin D-based cholecalciferol LD is required to achieve a 25-hydroxyvitamin D target level of at least 75 nmol/L according to the following equation: $LD \text{ (IU)} = 40 \times (75 - \text{baseline serum 25-hydroxyvitamin D level (nmol/L)}) \times \text{body weight (kg)}$. For the Noorderbreedte VDDR, a LD of 200,000 IU was calculated to be sufficient to obtain a vitamin D level ≥ 75 nmol/L in subjects with a body weight up to 75 kg and a serum vitamin D level as low as 10 nmol/L. A standardized LD of 200,000 IU was therefore considered adequate for the entire nursing home resident population regardless of initial serum 25-hydroxyvitamin D concentration. This way, there would be no need for the nursing home residents to undergo a blood drawing procedure to determine serum 25-hydroxyvitamin D status, and the nursing home staff would be able to administer the same first dose to each nursing home residents. Moreover, the long half-life of 25-hydroxyvitamin D allows for infrequent high-dose administration of cholecalciferol [16]. Following administration of a single oral dose of cholecalciferol 300,000 IU to men and women admitted to a geriatric hospital ward, 25-hydroxyvitamin D levels peaked between 13 and 21 days and declined with a half-life of 90 days [17]. It was therefore assumed that after an initial LD of 200,000 IU, a subsequent MD of 100,000 IU administered with a 3-monthly frequency would be sufficient to maintain a VDTL ≥ 75 nmol/L in the nursing home resident population included in this study. The standardized doses were to be administered by nursing staff on fixed

days, reducing the potential risk of medication errors to a minimum.

2.3 Endpoints and Measurements

The primary outcome for the efficacy of the VDDR was defined as the percentage of nursing home residents with a serum VDTL between 75 and 220 nmol/L. A one-time blood sample was drawn within 10 days prior to the next MD and subsequently analyzed for determination of the serum VDTL (liquid chromatography–tandem mass spectrometry [LC-MS/MS]; Roche Modular Analytics, Roche Diagnostics GmbH, Mannheim, Germany). Inter-assay coefficients of variation (CVs) were 5.1–7.5%. A secondary aim of this study was to assess a possible association between the VDDR and serum PTH and calcium levels (immunoassay and colorimetric assay, respectively; Roche Modular Analytics, Roche Diagnostics GmbH; inter-assay CVs 1.3–1.6% and 1.1–1.2%, respectively), and to identify predictive indicators for obtaining a VDTL ≥ 75 nmol/L. Serum calcium was corrected for serum albumin using the formula: $\text{corrected Ca} = \text{total Ca} + 0.02 (40 - \text{albumin})$. Hypercalcemia was defined as corrected Ca > 2.6 mmol/L. A serum PTH level > 6.9 pmol/L was referred to as hyperthyroidism. Data on age, sex, race, body weight and height, co-morbidity, co-medication, number of MDs, calcium supplementation, dairy intake, sunlight exposure (> 15 min/day between 11 a.m. and 3 p.m., leaving hands and head uncovered), care dependency status, smoking, and use of alcohol were obtained from patient charts, assuming these data would be registered consequently on structured forms.

2.4 Statistical Analysis

The VDDR was considered efficacious if at least 85% of nursing home residents obtained a VDTL 75–220 nmol/L. With a sample size of 150 subjects, this study had 91% power (target alpha 0.05) to detect a non-inferiority proportion of 0.75, assuming an actual proportion of 0.85. Allowing for a dropout rate of 25%, an allocation of at least 200 nursing home residents was required.

Baseline demographics were described using descriptive statistics. Clopper–Pearson confidence intervals (CIs) were applied for the primary outcome. Secondary outcomes were analyzed as dichotomous variables using binary logistic regression. Independent-samples *t*-tests were used to test for differences between group means of continuous variables. Statistical analysis was performed with IBM SPSS® Statistics for Windows (version 19.0, released 2010; IBM Corp., Armonk, NY, USA).

3 Results

The study was conducted from November 2015 until August 2016. The total number of residents in the 12 participating nursing homes at the time of selection was 984. Overall, 204 nursing home residents (21%) were selected to participate. Ultimately, 156 subjects (16% of the total number of nursing home residents) were included for further analysis and a subsequent chart review was completed in 138 cases. Figure 1 shows the inclusion and exclusion process.

Of the 156 included nursing home residents, 71% were female and the median age was 85 years (range 56–99 years). The median number of MDs was nine (range 1–20, interquartile range [IQR] 13). The baseline characteristics are presented in Table 1. In 91 (58%; 95% CI 50–66) of 156 nursing home residents, a VDTL of 75–220 nmol/L (reference range) was measured with a mean ($\pm$ standard deviation [SD]) of 81 ($\pm$ 28) nmol/L (median 78 nmol/L, range 13–150 nmol/L; Fig. 2). Four (3%) subjects still suffered from severe vitamin D deficiency (VDTL < 25 nmol/L), whereas vitamin D deficiency (VDTL 25–49 nmol/L) was identified in 16 (10%) nursing home residents and vitamin D insufficiency (VDTL 50–74 nmol/L) was present in 45 (29%) cases.

No subjects demonstrated a VDTL above the toxicity threshold of 220 nmol/L.

None of the nursing home residents were sufficiently exposed to sunlight, and data on dairy intake and care dependency status were inadequately recorded (no use of structured forms or inconsequent registration). Therefore, these variables were excluded from the analysis. Table 2 presents the results of the logistic regression analysis. The only variable found to be a significant predictive indicator for obtaining a VDTL $\geq$ 75 nmol/L in the univariate analysis was a higher number of MDs ($\geq$ 4 vs. < 4; odds ratio 2.7; 95% CI 1.4–5.3): 42% in the fewer than four MDs group (mean $\pm$ SD VDTL 73 $\pm$ 29 nmol/L) versus 67% in the four or more MDs group (mean $\pm$ SD VDTL 85 $\pm$ 27 nmol/L) reached a VDTL within the reference range. For the other variables, no significant association was found.

Hypercalcemia was measured (VDTL varying from 15 to 113 nmol/L) in eight nursing home residents (5%), but this finding was not associated with a higher VDTL.

Hyperparathyroidism was observed in 75 residents (48%). However, although the average VDTL for residents with hyperparathyroidism was lower than the average VDTL of nursing home residents with a PTH level within the reference range, this difference did not reach statistical significance (78.2 vs. 83.4 nmol/L; $p = 0.39$).

Fig. 1 Flow diagram of the inclusion and exclusion process. MD maintenance dose, VDDR vitamin D dosing regimen

Table 1 Baseline characteristics of the included nursing home residents

Variable	Median (range) or <i>n</i> (%) ^a
Age in years (<i>n</i> = 156)	85 (56–99)
Sex (<i>n</i> = 156)	
Male	46 (29)
Female	110 (71)
Race (<i>n</i> = 138)	
Caucasian	136 (99)
Other	2 (1)
Length of stay in days (<i>n</i> = 156)	892 (139–5130)
Weight in kg (<i>n</i> = 137) [median (range) ± SD]	75 (41–154) ± 16
Co-morbidity (<i>n</i> = 138)	
Hypertension	50 (32)
COPD	12 (8)
Type 2 diabetes mellitus	34 (22)
No. of co-morbidities ^b (<i>n</i> = 138)	
0	65 (47)
1	51 (37)
2	21 (15)
3	1 (1)
eGFR ^c in mL/min/1.73 m ² (<i>n</i> = 156)	58 (5–190)
< 15 (dialysis)	2 (1)
15–29	9 (6)
30–59	60 (38)
≥ 60	85 (54)
No. of medication orders (<i>n</i> = 156)	10 (2–23)

CKD-EPI Chronic Kidney Disease Epidemiology Collaboration, COPD chronic obstructive pulmonary disease, eGFR estimated glomerular filtration rate, SD standard deviation

^aUnless specified otherwise

^bOne or more of the following co-morbidities: hypertension, COPD, type 2 diabetes mellitus

^cCalculated from serum creatinine using the CKD-EPI equation

4 Discussion

With the standardized oral VDDR, 58% of the nursing home residents obtained a VDTL 75–220 nmol/L (reference range). The VDDR would be regarded efficacious if at least 85% of nursing home residents obtained a VDTL 75–220 nmol/L, whereas a percentage > 75% would be considered as non-inferior to the target of 85%. With an outcome of 58%, the VDDR is regarded as inefficacious. As no VDTL > 220 nmol/L was measured and the hypercalcemia found in 5% of nursing home residents was not associated with a higher VDTL, the VDDR did not exert biochemical toxicity. The hyperparathyroidism measured in 48% of subjects could not be attributed to a lower VDTL, suggesting another cause for this finding (e.g., low dietary calcium intake).

To date, no study has yet described a standardized oral cholecalciferol dosing regimen that was shown to be effective in achieving and maintaining an adequate and safe 25-hydroxyvitamin D level in nursing home residents over

a longer period of time [12–14, 18–31]. In the study by Tellioglu et al. [28] in which nursing home residents with a baseline 25-hydroxyvitamin D concentration < 75 nmol/L received a single oral dose of cholecalciferol 600,000 IU, 83.3% of the subjects had maintained a vitamin D level ≥ 75 nmol/L after 12 weeks [28]. However, such large doses might induce transient vitamin D intoxication in the first period after administration [32], and bolus doses of ≥ 100,000 IU are reported to significantly increase bone resorption markers in a dose-dependent fashion [5]. In addition, annual oral administration of cholecalciferol 500,000 IU resulted in an increased risk of falls and fractures among older community-dwelling women [33]. Moreover, a recent randomized controlled trial in elderly women reported a significant increase in the number of falls and fractures associated with serum levels of 25-hydroxyvitamin D greater than 100–112 nmol/L [34], suggesting a lower upper level as a safety threshold than the 220 nmol/L used in our study.

Fig. 2 Box plot showing median (central thick line), 25% and 75% quartile range (box), and upper and lower limits (whiskers) of measured vitamin D trough levels. The target serum 25-hydroxyvitamin D concentration of 75 nmol/L is indicated by the dotted line

The cross-sectional design of this study allowed for data collection from nursing home residents who had received one to 20 MDs, which provided insight into both the short- and long-term efficacy of the VDDR. In addition, our study demonstrates an association between the number of MDs and obtaining an adequate VDTL.

As hepatic vitamin D₃ hydroxylation may be saturable and excess vitamin D₃ is stored in fat depots at supraphysiologic intakes [1, 35], a possible explanation for our finding is that with continued cholecalciferol dosing at a constant frequency the slow release from adipose tissue might over time render a longer half-life of 25-hydroxyvitamin D, ultimately resulting in a higher VDTL. This phenomenon may also explain the wide variability in half-life reported in response to different doses of vitamin D supplementation in different study populations. Pharmacokinetic studies in humans given a single, large oral dose of cholecalciferol indicate that 25-hydroxyvitamin D displays a substantial variability in inter-subject half-life, ranging from 60 days in healthy community-dwelling men and women to 90 days in elderly inpatients [17, 36]. The need for administration of four or more MDs in order to obtain a VDTL ≥ 75 nmol/L in our study suggests a period of at least a year to reach steady state, implying a half-life of several months in our overall population. During the time to reach an adequate 25-hydroxyvitamin D level, however, subjects may experience suboptimal vitamin D levels and the health risks that accompany a low vitamin D status. The hypothesis underlying the VDDR,

however, was that vitamin D stores would be rapidly replenished by the LD and that prior to administration of the first MD an adequate VDTL would be attained. Assuming the population as a whole to be deficient, the LD of 200,000 IU might not have been sufficient to attain a VDTL ≥ 75 nmol/L after 3 months, as the standardized LD was calculated to obtain a vitamin D concentration ≥ 75 nmol/L immediately after administration. As no subject variables could be identified as predictive indicators for obtaining a VDTL ≥ 75 nmol/L, in which nursing home residents the VDDR will lead to adequate vitamin D levels cannot be predicted beforehand.

This study has several limitations. As the subjects who participated in the study were assigned by the elderly care physicians, the study population (16% of the total number of residents) could be more or less healthy and suffer from more or fewer co-morbidities as opposed to the remainder of the nursing home resident population (84% of the total number of residents), influencing vitamin D pharmacokinetics with an impact on serum 25-hydroxyvitamin D. Subjects were not screened for presence of gastrointestinal disorders that might have caused cholecalciferol malabsorption, leading to lower 25-hydroxyvitamin D levels. This could be an explanation for the 25-hydroxyvitamin D levels as low as 13 nmol/L.

Furthermore, as blood samples were drawn within 10 days prior to the next MD, an inter-subject variability in the 25-hydroxyvitamin D half-life and varying time interval between the administration of the last MD and the

Table 2 Results of the univariate logistic regression analysis on obtaining a serum 25-hydroxyvitamin D level ≥ 75 nmol/L

Variable	<i>n</i>	Category	<i>n</i>	Univariate analysis	
				OR	95% CI
Age (years) ^a	156	≤ 85	83	Ref.	
		> 85	73	0.9	0.5–1.8
Sex	156	Male	46	Ref.	
		Female	110	0.5	0.2–1.1
Race	138	Caucasian	136	Ref.	
		Other	2	0.6	0.0–9.8
Smoking	137	No	126	Ref.	
		Yes	11	3.0	0.8–14.3
Alcohol use	137	No	126	Ref.	
		Yes	11	2.6	0.5–12.7
Renal impairment ^b (eGFR < 60 mL/min/1.73 m ²)	156	No	85	Ref.	
		Yes	71	0.8	0.4–1.5
Hypercalcemia ^c (Ca > 2.60 mmol/L)	156	No	148	Ref.	
		Yes	8	1.2	0.3–5.2
Hyperparathyroidism (PTH > 6.9 pmol/L)	156	No	81	Ref.	
		Yes	75	0.8	0.4–1.6
Weight (kg) ^a	137	≤ 73.5	69	Ref.	
		> 73.5	68	0.7	0.3–1.4
BMI (kg/m ²)	105	< 30	86	Ref.	
		≥ 30	19	0.5	0.2–1.3
No. of maintenance doses	156	1–3	52	Ref.	
		≥ 4	104	2.7	1.4–5.3
No. of medications negatively associated with vitamin D levels	156	0	53	Ref.	
		$\geq 1^d$	103	1.1	0.6–2.7
Concurrent calcium supplementation	156	Yes	23	Ref.	
		No	133	1.3	0.6–3.3
No. of co-morbidities	138	0	59	Ref.	
		$\geq 1^e$	79	0.7	0.3–1.3
Previous vitamin D supplementation	156	Yes	72	Ref.	
		No	84	0.8	0.4–1.5

ATC Anatomical Therapeutic Chemical, BMI body mass index, Ca calcium, CI confidence interval, CKD-EPI Chronic Kidney Disease Epidemiology Collaboration, COPD chronic obstructive pulmonary disease, eGFR estimated glomerular filtration rate, OR odds ratio, PTH parathyroid hormone, Ref. reference (category)

^aDichotomous classification (median split)

^bCalculated from serum creatinine using the CKD-EPI equation

^cAll given calcium levels represent total calcium levels corrected for albumin (Ca_{corr}) according to the equation Ca_{corr}=total calcium + [0.02 × (40 – albumin)], expressed in mmol/L

^dOne or more of the following medications (ATC code): orlistat (A08AB01), diuretics (C03A, C03C), spironolactone (C03DA01), calcium channel blockers (C08C, C08D, C08E, C08G), bile acid sequestrants (C10AC), cyproterone (G03HA01), mifepristone (G03XB01), glucocorticoids (H02AB), rifampicin (J04AB02), isoniazid (J04AC01), protease inhibitors (J05AE), nucleoside and nucleotide reverse transcriptase inhibitors (J05AF), paclitaxel (L01CD01), tamoxifen (L02BA01), ciclosporin (L04AD01), tacrolimus (L04AD02), antiepileptics (N03A), glutethimide (N05CE01), antidepressants (N06A), metyrapone (V04CD01)

^eOne or more of the following co-morbidities: COPD, hypertension, cholecystectomy, type 2 diabetes mellitus

procedure of blood drawing could explain the wide range in observed VDTLs, with subjects displaying a shorter half-life and longer MD administration–blood drawing interval demonstrating a lower VDTL.

Another limitation of this study is that no baseline 25-hydroxyvitamin D levels were measured. Therefore, the VDDR-induced increment in vitamin D concentration could not be quantified. Moreover, as nursing home

residents who had received vitamin D supplementation of cholecalciferol ≤ 800 IU/day prior to administration of the VDDR were not excluded from the study, it cannot be ruled out that their baseline 25-hydroxyvitamin D levels were higher than those of subjects who had not received previous cholecalciferol supplementation. Several studies have shown a significant inverse correlation between the baseline serum vitamin D concentration and response to vitamin D supplementation, suggesting the achieved increment to be higher with smaller doses as the administration of supraphysiologic amounts of cholecalciferol may lead to incomplete hepatic conversion to 25-hydroxyvitamin D [35, 37]. Large bolus doses may therefore be ineffective in rapidly normalizing vitamin D deficiency in subjects already replete prior to supplementation [37]. This concept supports an individualized dosing strategy based on baseline 25-hydroxyvitamin D levels and divided administration of the LD. However, as the drawing of blood and subsequent analysis of 25-hydroxyvitamin D is an invasive and costly procedure and the administration of a different dose in each subject may lead to medication errors, a standardized VDDR without the need to assess initial vitamin D status is preferred in the frail population of nursing home residents. In the study by Wijnen et al. [14], a total of 30 nursing home patients with 25-hydroxyvitamin D levels < 50 nmol/L were included and randomized to receive a daily dose regimen of 800 IU, or an individualized cholecalciferol LD regimen based on baseline 25-hydroxyvitamin D level and weight. The median calculated LD dose amounted to 235,754 IU (IQR 184,534–251,194) and was administered in divided doses of 50,000 IU twice a week followed by a monthly MD of either 50,000 or 25,000 IU. After 5 weeks, 11 of 14 LD subjects (79%) obtained a 25-hydroxyvitamin D level > 75 nmol/L and this result was maintained in ten of 12 LD subjects (83%) after 26 weeks. The individualized LD regimen was shown to be superior to the 800 IU daily dose, but no difference was found between the two monthly MDs. This study was limited by the small sample size.

As an alternative strategy to infrequent high-dose administration, daily supplementation of lower cholecalciferol doses could prove to be efficacious in obtaining the desired serum 25-hydroxyvitamin D level. The VDDR in our study corresponds to circa 1100 IU/day. However, to raise the serum 25-hydroxyvitamin D level above 75 nmol/L, at least 1500–2000 IU/day of cholecalciferol may be required [8].

Future research in nursing home residents should focus on establishing the optimal LD for acquiring a safe but adequate 25-hydroxyvitamin D level (the LD should be high enough to ensure that the 25-hydroxyvitamin D level is above the target value until the next dose is administered) and to determine the subsequent optimal MD and corresponding frequency in order to maintain an adequate VDTL.

5 Conclusion

Defining the optimal 25-hydroxyvitamin D level as 75–220 nmol/L, a standardized oral VDDR consisting of a single LD of cholecalciferol 200,000 IU followed by a MD of 100,000 IU every 13 weeks was not efficacious in obtaining and maintaining an adequate VDTL in a nursing home resident population in this study.

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Compliance with Ethical Standards

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Conflict of interest Marlous Toren-Wielema, Ruth Veenhuizen, Jan Willem Kappelle, Nic Veeger, and Eric van Roon declare that they have no conflicts of interest related to the content of this study.

Ethical approval Formal ethical approval for this study was waived according to Dutch national law.

Informed consent No individual-level informed consent was required for this study.

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