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VITAMIN D SUPPLEMENTATION AND INCIDENT FRAILTY IN OLDER PEOPLE: AN EIGHT YEAR LONGITUDINAL STUDY

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Abstract

Hypovitaminosis D is associated with frailty, but if vitamin D supplementation may prevent the onset of frailty is poorly known. Therefore, we aimed to investigate whether vitamin D supplementation is associated with a lower risk of frailty. In this longitudinal study, 4,421 individuals at high risk or having knee osteoarthritis free from frailty at baseline (mean age: 61.3, females=58.0%) were followed for 8 years. Details regarding vitamin D supplementation were

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captured by asking whether the participant took vitamin D during the previous year, at least once per month. Frailty was defined using the Study of Osteoporotic Fracture (SOF) index as the presence of at least two of the following criteria: (i) weight loss ≥5% between baseline and any subsequent follow-up visit; (ii) inability to do five chair stands; (iii) low energy level according to the SOF definition. Multivariable Cox's regression analyses, calculating hazard ratios (HRs) with 95% confidence intervals (CIs), were undertaken. At baseline 69.7% took vitamin D supplements in the previous year, with a mean dose of 384±157 IU per day. During the 8-year follow-up, no difference in the incidence of frailty was evident by vitamin D supplementation status at baseline, even after adjusting for 13 baseline confounders (HR=0.95; 95%CI: 0.72–1.25). Similar results were obtained using the propensity score (HR=0.95; 95%CI: 0.71–1.25) or age- and sex-matched controls (HR=1.00; 95%CI: 0.75–1.33). In conclusion, vitamin D supplementation was not associated with any decreased risk of frailty during eight years of follow-up in a large cohort of North American people. Future large-scale trials with high doses of oral vitamin D and longer follow-up are needed to confirm/refute our findings.

Keywords

frailty; vitamin D; older adults; Osteoarthritis Initiative

INTRODUCTION

Frailty is a measurable clinical syndrome that identifies persons at increased vulnerability to stress and who may have treatable conditions[1]. It has been associated with an increased risk of several deleterious outcomes, including disability, falls, hospitalization, institutionalization, and death[2]. It is assumed that early interventions for frailty might improve quality of life, reduce adverse outcomes, and associated costs of care[3].

The pathophysiology of frailty is complex and multi-factorial. However, nutrition is an important factor in its onset and a specific target for treatment[4,5]. The discovery that a variety of tissues can express vitamin D receptors has opened new venues for research related to the biological effects of vitamin D, also in terms of its effect on frailty. The connection between vitamin D and frailty may be explained by the effect of vitamin D on bone health and muscle strength[6] or through the association between vitamin D and comorbidities[7] strongly associated with frailty, such as depression[8] and dementia[9].

Vitamin D deficiency is generally associated with poor physical performance and some literature suggests that it could be predictive of incident mobility disability[10]. The association between low vitamin D status (defined as low serum 25-hydroxyvitamin D [25(OH)D]) and frailty has been evaluated in several studies. In a large cross-sectional study including 5,000 elderly Americans, Wilhelm-Leen et al. found a significant association between low vitamin D status and frailty[11]. Similarly, many other cross-sectional studies reported that low vitamin D is associated with frailty[12–14]. However, there is less longitudinal data suggesting that poor vitamin D status is associated with an increased risk of developing frailty and the data are equivocal. For example, in a prospective study including elderly women, subjects with lower serum vitamin D levels at baseline had a

higher risk of becoming frail during 4.5 years of follow-up[15]. Similar findings were also reported in elderly men[14]. Conversely, Schöttker et al. found no association in another longitudinal study, suggesting that low serum 25(OH)D levels are probably more likely to be an useful biomarker of poor health in the elderly than a cause[16]. Finally, a recent systematic review with meta-analysis found that people having low serum 25(OH)D levels had an increased odds of frailty[17]. Interventional studies have investigated the effect of vitamin D supplementation on muscle function, finding, again, controversial results. Some of them reported a benefit of vitamin D supplementation on muscular strength and performance[18–20], while others did not report such an effect[21,22]. However, to the best of our knowledge, no previous study has investigated the potential relationship between vitamin D supplementation and frailty development.

Given this background, the aim of the present study was to investigate the association between vitamin D oral supplementation at baseline and the onset of frailty in a large cohort of North American people, over a follow-up of 8 years. Since previous literature has reported that vitamin D supplementation is effective in improving muscle strength and performance, we hypothesized that subjects who take oral supplementation will be at lower risk of frailty development over time.

METHODS

Data source and subjects

Data were obtained from the Osteoarthritis Initiative (OAI) database, available for public access at http://www.oai.ucsf.edu/. The specific datasets utilized were registered during the baseline and screening evaluations (V00) and each database reporting data on frailty until 96 months from baseline (V10). Patients at high risk of knee OA were recruited at four clinical centers in the USA (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006. For this study, the specific exclusion criteria were: presence of rheumatoid arthritis, bilateral total knee joint replacement or plans to in the next 3 years, unable to undergo a magnetic resonance investigation, positive pregnancy test, unable to provide a blood sample for any reason, use of ambulatory aids for walking, co-morbid conditions that can interfere with the study's outcomes, unlikely to reside in the clinic area for at least 3 years, unwilling to sign an informed consent. All the participants provided written informed consent. The OAI study protocol was approved by the institutional review board of the OAI Coordinating Center, University of California at San Francisco.

Baseline vitamin D supplementation (exposure)

A specific questionnaire investigating the name of the prescription medicine or nutritional supplementation, duration of use, formulation code in the 30 days before the interview was used. A trained interviewer asked whether the participant had taken any vitamins or minerals regularly, at least once per month, during the previous year. A similar question was used during the follow-up controls, i.e. at visits 3, 5, 6, 8, and 10 and included in the analysis as time dependent variable. Vitamin D supplementation was also categorized in terms of daily consumption (<200 international units (IU), 200–400 IU, and 400–600 IU per day).

Incident frailty (outcome)

The study's outcome of interest was incident frailty. Frailty was assessed as outcome at wave 1, 3, 5, 6, 8 and 10. In accordance with the Study of Osteoporotic Fracture (SOF) index[23–25], frailty was defined as the presence of at least 2 of the following 3 criteria: (i) weight loss ≥5% taking place between baseline and any follow-up examination (since no information regarding weight changes were available at baseline, we considered those with a body mass index (BMI) <20 Kg/m^2 to fulfill this criteria only for baseline); (ii) the inability to rise from a chair five times without arm support (hereafter referred to as inability to carry out chair stands); and (iii) poor energy based on the SF12 questionnaire. Specifically, a response of "little at a time" or "none at a time" to the question "in the past 4 weeks, did you feel full of energy?"

Covariates

Other than the number frailty criteria at baseline (categorized as one vs. none), we identified several potential confounders at baseline in the association between vitamin D supplementation and frailty including BMI (measured by a trained nurse); physical activity evaluated using the Physical Activity Scale for the Elderly (PASE)[26]; depressive symptoms evaluated through the Center for Epidemiologic Studies Depression Scale[27]; race (Caucasian vs. others); smoking habits (actual/previous vs. never smokers); educational level (college degree vs. below) and yearly income (< or ≥ $50,000 or missing data). Validated general health measures of self-reported comorbidities (heart attack, heart failure, peripheral artery disease, stroke, asthma, chronic obstructive pulmonary disease, peptic ulcer, diabetes, poor kidney function, polymyalgia rheumatica, cirrhosis, cancer) were assessed using the modified Charlson comorbidity score.[28] Since nutritional parameters could also be of importance to assess the association between vitamin D supplementation and incident frailty[29], we also included as covariates the daily calorie and vitamin D intake from foods.

Statistical analyses

Normal distributions of continuous variables were tested using the Kolmogorov-Smirnov test. Data are shown as means±standard deviations (SD) for quantitative measures, and percentages for all discrete variables. The difference in baseline characteristics between those with and without vitamin D supplementation was tested by the independent T-test for continuous variables and Chi-square test for categorical ones.

Cox's regression analysis was used to assess the strength of the association between vitamin D supplementation at baseline and the onset of frailty during follow-up. Factors significantly different between those consuming vitamin D or not (considering a p-value<0.10) or significantly associated with incident frailty at univariate analysis (p-value<0.05) were included. Multi-collinearity among covariates was assessed using the variance inflation factor (VIF), with a score of 2 leading to the exclusion of a variable, but no parameter was excluded for this reason. The compliance between baseline and follow-up visits (3, 5, 6, 8, and 10) was also ascertained through the same questionnaire of the baseline.

The basic model was adjusted for age and sex. In the fully-adjusted model the variables used were: age (as continuous); sex; race (Caucasian vs. others); BMI (as continuous); education

(college degree vs. below); smoking habits (current and previous smokers vs. others); yearly income (categorized as ≥ or < 50,000$ and missing data); Physical Activity Scale for Elderly score (as continuous); Charlson co-morbidity index (as continuous); Center for Epidemiologic Studies Depression Scale (as continuous); number of frailty indexes at baseline (one vs. none); total energy intake (in Kcal/day); vitamin D intake from foods (in international units/day). The proportional hazard assumption was verified considering Schoenfeld's residuals of the covariates[30]. Cox's regression analysis estimates were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). A similar analysis was run using vitamin D supplementation categorized as <200, 200–400, >400 IU/day with those not taking any vitamin D supplements as the reference. Finally, we also assessed the relationship between total daily vitamin D intake (supplementation and diet) and the onset of frailty during follow-up. The interaction between vitamin D supplementation at baseline and selected baseline factors in the association with frailty was also investigated. These factors included age (<65 vs. ≥65 years), BMI [overweight/obese (BMI≥25kg/m^2) vs. normal weight (BMI 18.5–24.9kg/m^2)], yearly income, gender, race, education, smoking habits, yearly income, number of frailty index (one vs. none), and presence vs. people at high risk of knee osteoarthritis.

Finally, in order to assess the robustness of our findings, we conducted further analyses using the propensity score[31] which was estimated by using a logistic regression model regressing baseline vitamin D supplementation use on the above-mentioned baseline covariates. We also conducted a case-control investigation where 1,300 participants taking vitamin D supplements were compared with 1,300 sex- and age-matched controls not taking vitamin D supplements. The covariate balance for the treated and matched control groups was tested by Student's independent *t*-tests and Chi-squared tests for continuous and categorical variables, respectively. Multivariable Cox regression analysis adjusting for the propensity score using the overall sample, and an analysis (adjusted for all the covariates included in the fully-adjusted model) using the matched controls were conducted to assess the association between vitamin D supplementation and incident frailty.

All the analyses were performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed and statistical significance was assumed for a p-value <0.05.

RESULTS

Sample selection

The OAI dataset initially included a total of 4,796 North American participants. Twenty-two participants were excluded since they were already frail at baseline. Another 353 were excluded since they did not provide data regarding incident frailty. Thus, 4,421 participants constituted the final sample.

Descriptive characteristics

Of the 4,421 participants, 1,857 were males and 2,564 females. The mean age across the entire sample was 61.3 years (±9.2 years; range: 45–79). As shown in Table 1, more than

two thirds of the participants (69.7%) took vitamin D supplements in the previous year, with a mean dose of 384±157 IU per day (range: 57–600 IU/day). The mean total daily vitamin D consumption (supplementation and diet) was 143±108 IU (range: 3–1286 IU).

Table 1 shows the participants' characteristics by vitamin D supplementation status. The 3,083 participants taking vitamin D supplements were significantly more likely to be older, females, and Caucasian ($p<0.0001$ for all comparisons). Those taking vitamin D supplements were significantly leaner ($p<0.0001$) with less depressive symptoms ($p<0.0001$), whilst they did not differ in terms of presence of co-morbidities ($p=0.69$). Regarding nutritional items, people taking vitamin D supplements had a significant lower total energy intake ($p<0.0001$), but a higher intake of vitamin D from foods ($p=0.003$) (Table 1). Regarding frailty items at baseline, we observed that people taking vitamin D supplements had a marginally significant higher prevalence of poor physical performance (2.5 vs. 1.6%, $p=0.05$), but no differences emerged in terms of poor chair stands time ($p=0.09$) or weight loss ($p=0.34$) (Table 1).

Vitamin D supplementation and incident frailty

During the 8-year follow-up, 362 subjects (8.2% of the baseline population) developed frailty corresponding to a global incidence rate of 12 (95%CI: 10–13)/1,000 persons-year. Among the singular criteria, the most frequent was poor chair stands time (n=780, 17.6%), followed by poor physical performance (n=503, 11.4%) and weight loss (n=19, 0.4%). The incidence of new cases of frailty was similar between people taking vitamin D supplementation at baseline (cumulative: 254/3,083=8.2%; incidence rate: 11/1,000 persons-year; 95%CI: 10–13) and those not (cumulative: 108/1,338=8.1%; incidence rate: 12/1,000 persons-year; 95%CI: 10–14) ($p=0.84$).

Table 2 shows the association between vitamin D supplementation at baseline and incident frailty at follow-up. Taking no vitamin D supplementation at baseline as the reference, and after adjusting for 13 potential baseline confounders, the supplementation of vitamin D was not associated with any reduced risk of incident frailty during follow-up (HR=0.95; 95%CI: 0.72–1.25; $p=0.70$). No interaction was observed between vitamin D supplementation and any of the selected confounders considered. We further divided the amount of vitamin D consumption via supplements into three categories to assess whether higher doses are protective of frailty. However, taking people without vitamin D supplementation as the reference, no significant associations were observed with increasing doses of vitamin D [fully-adjusted HR for those consuming <200 IU/daily (669 participants; 1.08; 95%CI: 0.78–1.51; $p=0.64$); 200–400 IU (1571 participants; 0.97; 95%CI: 0.74–1.27; $p=0.83$); >400 IU (843 participants; 1.20; 95%CI: 0.88–1.64; $p=0.26$)] (data reported only in text). Finally, we assessed whether total vitamin D intake (supplementation and diet) could predict the onset of frailty during follow-up. Each increase in 200 IU in total vitamin D intake was, however, not associated with any reduced risk of frailty (HR=1.03; 95%CI: 0.66–1.60; $p=0.91$) also in terms of the comparison between the highest vs. the lowest groups (HR=1.01; 95%CI: 0.68–1.74; $p=0.42$) (data shown only in text). Finally, comparing the 696 participants taking 600 IU/day vs. the other participants did not significantly change our results (HR=1.36; 95%CI: 0.95–1.80; $p=0.28$).

In Table 2, we also report other secondary analyses to further assess potential confounding in the relationship between vitamin D supplementation at baseline and incident frailty. Using a cohort of 1,300 people taking vitamin D supplements matched for age and sex with 1,300 controls, the fully-adjusted HR was 1.00 (95%CI: 0.75–1.33; p=0.99). Similar results were evident using the propensity score (HR=0.95; 95%CI: 0.71–1.25; p=0.69) (Table 2).

DISCUSSION

In the present study involving a large number of persons living in North America, we found that vitamin D oral supplementation is not associated with a reduction of incident frailty over eight years of follow-up. This non-significant finding remained unaltered after adjustment for potential confounders, the use of a matched control, or propensity score adjustment.

At baseline, people taking vitamin D oral supplements were significantly older and more frequently women than those not taking vitamin D. Moreover, people taking vitamin D presented a lower BMI and calorie intake. All these factors might, however, increase (and not decrease) the risk of frailty. These findings were expected, as vitamin D supplementation is known to be more common in older women than men or younger subjects[32–34], primarily for a high prevalence of low vitamin D status[35] and clinical conditions such as osteopenia or osteoporosis in the postmenopausal period[36]. The finding that persons with higher BMI had a lower percentage of vitamin D oral supplementation is probably also related to their higher bone mineral density values. The protective effects of higher BMI may result from increased chronic strain on the bones and an increased production of estrogens from larger stores of adipose tissue[37], with consequent higher bone mass index[38]. Persons taking vitamin D supplements also had poorer physical performance at baseline. Known low vitamin D status, a possible marker of poor health in general[7], may have prompted these individuals to take vitamin D supplements. We addressed potential confounding by these factors using several methods including the use of age- and sex- matching and the propensity score[39], but the association between vitamin D supplementation and frailty remained non-significant.

To the best of our knowledge, this is the first study on the association between vitamin D supplementation and frailty development. Our findings were somewhat unexpected considered the findings from previous studies on vitamin D supplementation and physical performance. For example, Zhu et al. reported a positive association between low vitamin D status or vitamin D supplementation for one year and muscle strength in older women[19]. However, in this study, the subjects received a large amount of vitamin D (1000 IU/day). Moreover, the benefits were limited to those women who were the weakest and slowest at baseline[19]. Similarly, an Asian study in elderly women demonstrated a positive effect of weekly vitamin D supplementation on quadriceps strength during 3 to 6 months of follow-up. In this study, however, only old women with low vitamin D status (25(OH)D <30 ng/ml) were enrolled[18]. Even in a group of elderly institutionalized elderly patients, an oral supplementation of 3600 IU/day of vitamin D for 6-month improved muscle strength in lower limbs[40]. Moreover, a daily supplementation of 1000 IU/d of vitamin D for 9 months has been shown to be a protective factor against the occurrence of sarcopenia, with an important increase in muscle strength and control of the progressive loss of lean mass in a

group of Brazilian postmenopausal women[41]. Finally, one meta-analysis including only RCTs on vitamin D supplementation found that vitamin D supplementation significantly increases upper and lower limb strength in younger people compared to placebo[42], whilst a more recent work found no improvement in muscle strength after the administration of vitamin D with or without calcium supplements in older participants[43].

We can argue that, even if these trials advanced our knowledge regarding the impact of vitamin D oral supplementation and physical performance, the short follow-up (less than one year) could influence the results of these interventional studies. An explanation for our discrepant findings could be related to the higher dose of vitamin supplementation used in these trials and the fact that the majority of the subjects enrolled had a defined low vitamin D status[44] or were already frail at baseline. In fact, other studies on vitamin D supplementation and muscular function agree with our results. Kenny et al. found no improvement in physical performance, muscle strength or health perception in a group of old healthy man taking a daily supplementation of 1000 IU of cholecalciferol[22]. Likewise, in a Dutch study in old women, a dose of oral vitamin D supplementation similar to our study (400 UI/day), did not significantly improve strength or mobility. The authors concluded that maybe this amount of supplementation was not enough to achieve the targets.[45]

The present findings should be considered within the limitations of the study. First, we had no data about vitamin D status evaluated through serum 25(OH)D levels. Thus, it was not possible to elucidate a possible effect on frailty development when restricted to people with insufficient serum levels of 25OH vitamin D at baseline. Second, in the group of subjects taking oral vitamin D supplementation, the mean amount of vitamin D taken was only 384 IU/d, which was probably not enough to achieve the target, considering that previously reported interventional studies administered supplementations of 1000 IU/d or above. However, in contrast to RCT settings, our study represents the findings of a real-world population. Finally, we used a slightly different definition of frailty at baseline with respect to the one used at the follow-up as far as weight loss was concerned. Using that definition, only 20 participants were considered frail at baseline. Unfortunately, no data regarding weight changes were available in the OAI at baseline and it is possible that some frail individuals at baseline were included in our analysis.

In conclusion, the oral supplementation of vitamin D was not associated with decreased risk of frailty during eight years of follow-up in a large cohort of North American people. Despite our results, future studies taking incident frailty as outcome are warranted to assess whether vitamin D supplementation could be associated with a lower incidence of frailty over time.

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- Vitamin D seems to be beneficial for muscular performance in older people.
- The data regarding frailty are still limited.
- In our study, vitamin D supplementation did not reduce the risk of frailty.
- Future RCTs with this aim are needed.

Table 1

Characteristics of the participants according to baseline vitamin D supplementation status.

	Vitamin D supplementation (n=3083)	No vitamin D supplementation (n=1338)	p-value[a]
General characteristics			
Age (years)	62.1 (9.1)	59.5 (9.2)	<0.0001
Females (n, %)	1970 (63.9)	594 (44.4)	<0.0001
PASE (points)	159.9 (82.0)	163.4 (83.0)	0.20
Caucasian race (n, %)	2592 (84.1)	961 (71.9)	<0.0001
Smoking (previous/current) (n, %)	1420 (46.3)	657 (49.3)	0.07
College degree (n, %)	962 (31.2)	384 (28.8)	0.11
Yearly income (≥ $50,000)	1842 (59.7)	775 (57.9)	0.26
Medical conditions			
BMI (Kg/m^2)	28.3 (4.7)	29.4 (4.9)	<0.0001
CES-D (points)	6.2 (6.4)	7.3 (7.8)	<0.0001
Charlson co-morbidity index (points)	0.4 (0.8)	0.4 (0.9)	0.69
Nutritional items			
Total energy intake (Kcal/day)	1391 (544)	1466 (617)	<0.0001
Vitamin D (from supplementation) (IU/day)	384 (157)	-	-
Vitamin D (from foods) (IU/day)	145 (110)	134 (104)	0.003
Frailty items			
Poor physical performance (n, %)	78 (2.5)	21 (1.6)	0.05
Poor chair stands time (n, %)	325 (10.5)	165 (12.3)	0.09
Weight loss (n, %)	25 (0.8)	7 (0.5)	0.34

Notes: The data are presented as means (with standard deviations) for continuous variables and number (with percentage).

[a]P values were calculated using the independent T-test for continuous variables and Chi-square test for categorical ones.

Abbreviations: CES-D: Center for Epidemiologic Studies Depression Scale; PASE: Physical Activity Scale for the Elderly; BMI: body mass index; IU: international units.

Table 2

Multivariable proportional hazard regression models on the effect of vitamin D supplementation at baseline on incident frailty.

	HR	95% CI	*p* - value
Without matching			
No vitamin D supplementation	1		
Vitamin D supplementation (basic model)	0.85	0.67–1.07	0.17
Vitamin D supplementation (fully-adjusted model)	0.95	0.72–1.25	0.70
Age and sex matched controls			
No vitamin D supplementation	1		
Vitamin D supplementation (basic model)	-	-	-
Vitamin D supplementation (fully-adjusted model)	1.00	0.75–1.33	0.99
With propensity score matching			
No vitamin D supplementation	1		
Vitamin D supplementation (basic model)	-		
Vitamin D supplementation (fully-adjusted model)	0.95	0.71–1.25	0.69

Abbreviations: HR: hazard ratio; CI: confidence interval.

Basic model includes age (as continuous) and sex.

Fully adjusted model included as covariates: age (as continuous); sex; race (caucasian vs. others); body mass index (as continuous); education (college degree vs. others); smoking habits (current and previous smokers vs. others); yearly income (categorized as ≥ or < 50,000$ and missing data); Physical Activity Scale for Elderly score (as continuous); Charlson co-morbidity index; Center for Epidemiologic Studies Depression Scale (as continuous); number of frailty indexes at baseline (one vs. none); total energy intake (in Kcal/day); vitamin D intake from foods (in international units/day).