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MAJOR ARTICLE

Vitamin D and Acute Respiratory Infections—The PODA Trial

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Background. There is considerable heterogeneity in clinical trials examining the role of vitamin D in the prevention of acute respiratory infections (ARIs).

Methods. The primary aim of the Physical Performance, Osteoporosis, and Vitamin D in Older African-American Women (PODA) trial was the prevention of bone loss and decline in physical performance. A questionnaire about ARIs was administered every 3 months for 3 years to 260 black American women in a double-blind randomized clinical trial that had a placebo group and a vitamin D supplementation group. The serum 25(OH)D level was maintained >30 ng/mL in the vitamin D group.

Results. Serum 25(OH)D was maintained >30 ng/mL in 90% of the active group, whereas levels approximated those associated with the recommended dietary allowance (20 ng/mL) in the placebo group. There was no difference in occurrence of ARIs in the treatment group vs the placebo group. ARIs were not related to total or free 25(OH)D, which were measured at baseline and annually for 36 months.

Conclusions. Vitamin D supplementation sufficient to maintain serum 25(OH)D >30 ng/mL does not prevent ARIs in older African American women.

ClinicalTrials.gov Registration Number. NCT01153568.

Keywords. acute respiratory infection; osteoporosis; vitamin D; vitamin D metabolites.

As there is seasonality in acute respiratory infections (ARIs), it has been suggested that vitamin D (which changes with sun exposure) may prevent them [1]. There is biologic plausibility for this suggestion because of the relationship between vitamin D and the immune system. In a post hoc analysis of adverse events in a vitamin D trial of prevention of bone loss in African American women we noted that more than 3 times reported cold influenza episodes in the placebo group compared with the vitamin D treatment group. [2] We subsequently performed a randomized clinical trial to determine if vitamin D could prevent ARIs. One hundred sixty-two adults were randomized to receive either placebo or 50 μg of vitamin D_3 (2000 IU) daily for 12 weeks during winter. We found no difference in events or severity of ARIs between groups. [3] Subsequently, there have been numerous clinical trials (25 evaluable in a recent meta-analysis) and several meta-analyses concerning this issue, with heterogeneity in their results [3–23].

The Physical Performance, Osteoporosis, and Vitamin D in Older African-American Women (PODA) trial had as its primary outcomes the prevention by vitamin D of bone loss and decline in physical performance in older black women [24]. A secondary aim was to determine if vitamin D prevented acute respiratory infections during this 3-year randomized clinical trial (RCT). There is considerable controversy concerning optimal serum 25(OH)D to achieve beneficial effects of vitamin D. The Institute of Medicine in 2011 set the recommended dietary allowance (RDA)-associated 25(OH)D level at 20 ng/mL, whereas the Endocrine Society Guidelines recommend achieving levels >30 ng/mL [25–27]. This report is an analysis of the impact of vitamin D supplementation designed to maintain serum 25(OH)D >30 ng/mL on the incidence of ARIs in the PODA trial.

METHODS

The PODA study is a prospective, randomized, double-blind, placebo-controlled, 3-year clinical trial of vitamin D_3 supplementation in black American women older than 60 years of age. The primary aim of this trial was to determine if maintenance of serum 25(OH)D at levels recommended by the Endocrine Society (>30 ng/mL) was protective against loss of bone density and physical performance with aging. The study design and results of bone density, physical performance, cognition, and falls have been previously reported [24, 28–31]. Participants were self-declared as black. Written informed consent was obtained

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from each participant, and the trial was approved by the Winthrop Institutional Review Board and monitored by a Data Safety Monitoring Board appointed by the National Institute of Aging. The trial was registered at www.clinicaltrials.gov as NCT011533568.

Healthy participants were recruited from the Long Island community by direct mail, email to hospital employees, and presentations at black churches and events. The study was conducted in an ambulatory Clinical Research Center of an academic health center. After screening, those who consented and qualified were randomly allocated to 1 of 2 groups: vitamin D supplementation or placebo. Inclusion criteria were healthy ambulatory women who were self-declared as black Americans, with serum 25(OH)D >8 ng/mL and <26 ng/mL. Participants returned for follow-up visits every 3 months for 36 months. A questionnaire concerning upper respiratory infections was administered by the research coordinator at each visit.

Fasting blood samples were collected at baseline and at 3-monthly visits. Serum samples for measurement of 25OHD and $1,25(OH)_2D$ at baseline and annually were analyzed by the Department of Laboratory Medicine at the University of Washington (Seattle, WA) using liquid chromatography–tandem mass spectrometry with deuterated internal standards for each analyte [32]. Concentrations of 25(OH)D were standardized to National Institute of Standards and Technology SRM 972a [33]. Serum-free 25OHD was directly measured using enzyme-linked immunosorbent assay based on a 2-step immunoassay procedure (Future Diagnostics, Wijchen, the Netherlands), as previously described [34, 35]. Markers of bone turnover and parathyroid hormone (PTH) levels were measured in serum at baseline and at 6-month intervals. Intact PTH was measured by the Immulite 2000 Analyzer assay (Diagnostic Products Corporation, Los Angeles, CA; interassay CV: 1.34%).

Statistical Methods

Block randomization with a block size of 4 was performed at baseline using a computer-generated (SAS Proc Plan; SAS Institute, Inc., Cary, NC) randomization list. Subjects were assigned to 1 of 2 groups: vitamin D_3 supplementation or placebo. Any participants who were randomized and received at least 1 dose of study medication were included in the intention-to-treat (ITT) population, and primary analysis was performed according to the ITT principle. In the original study design, power was determined based on previous studies and a differential bone mineral density rate of change of ≥0.18% per year.

Descriptive statistics were generated and presented as mean ± standard deviation or median (interquartile range) for continuous variables and frequency (percentage) for the categorical variables. Normality of distribution of clinical variables and laboratory markers was examined using visual inspection of histograms and the Kolmogorov-Smirnov test. Between-group differences for each continuous variable were examined using the nonparametric Wilcoxon rank-sum test for non–normally distributed variables and the 2 independent-samples *t* test for normally distributed variables. Variables were checked for outliers, and analyses were performed with and without outliers, but output remained similar, so full data were used. The Fisher exact test was used to compare categorical variables between groups.

ARI data were gathered from the following question: "How many times did you have a cold or flu?" Answer choices were "none," "1 to 2," or "3 to 4" times. Data were collected at each 3-month visit. There were only a few subjects with 3 to 4 events (n = 9 events). Therefore, the "1 to 2" and "3 to 4" categories were combined. Essentially, a variable was re-coded as with 1 = had ARI since last visit and 0 = did not have ARI since the last visit.

The difference in ARI rate between treatment groups over time was evaluated using a repeated-measures mixed-effects logistic regression model. A random subject-specific intercept and an unstructured correlation structure were used to account for within-subject correlation between ARI rates overtime. Model fit was assessed using fit statistics such as AIC and Pearson chi-square/degrees of freedom. Associations of ARI with 25(OH)D, Free25(OH)D, 1,25(OH)D, PTH, serum creatinine, physical activity (measured as caloric expenditure), over time were also evaluated using mixed-effects logistic regression models. All calculations were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC). Results were considered statistically significant at a *P* value of <.05.

RESULTS

Baseline Demographics, Laboratory Studies, and Adherence

The average age was 68.2 years, and the BMI was 30 kg/m^2 (Table 1). There were no statistically significant differences in baseline characteristics between assigned groups. The mean dose of vitamin D_3 in the active arm was 3490 (±1465) IU/d.

Values (mean ± SD) for 25(OH)D at 12, 24, and 36 months in the active group were 43 ± 9.1, 46 ± 11.0, and 47 ± 11.2 ng/mL, respectively. Corresponding values for the placebo group were 19 ± 8.0, 20 ± 7.9, and 21 ± 10.0 ng/mL. Ninety percent of the active group maintained serum 25(OH)D above the 30-ng/mL threshold. Serum calcitriol increased by 10% at 36 months in the treatment group. Serum calcium did not change in either group. Overall compliance from pill count was 85% for the entire study.

Flow Diagram

A flow diagram for the study is given in Figure 1 [30]. The first participant was randomized on December 8, 2010, and the last 36-month visit was June 13, 2016. In the placebo group, there were 41 dropouts. In the vitamin D group, there were 33 dropouts; 1 subject had primary hyperparathyroidism. One subject in the placebo group died due to cardiorespiratory failure. Eighty-nine subjects in the placebo group and 95 subjects in the vitamin D group completed the 36-month study.

Table 1. Demographics and Baseline Characteristics

	Active (n = 130)	Placebo (n = 130)	Overall (n = 260)	P^a
Demographics and behavioral				
Age, y[b]	67.8 (65.1–71.5)	69.0 (65.4–73.4)	68.2 (65.4–72.5)	.251
BMI, kg/m^2[b]	30.2 (26.4–34.6)	30.0 (26.8–33.9)	30.1 (26.6–34.1)	.867
Calcium intake, mg[b]	842.0 (600–1142)	826.5 (628.0–1185)	828.0 (614.0–1164)	.857
Laboratory				
25(OH)D3, ng/mL	21.5 ± 6.5	22.2 ± 6.9	21.8 ± 6.7	.352
PTH, pg/mL[b]	56.1 (41.0–73.6)	56.4 (39.5–73.8)	56.2 (39.8–73.8)	.977
Serum Ca, mg/dL[b]	9.5 (9.3–9.8)	9.5 (9.3–9.8)	9.5 (9.3–9.8)	.943
Serum Cr, mg/dL[b]	0.8 (0.7–0.9)	0.7 (0.6–0.9)	0.8 (0.6–0.9)	.472
Free 25(OH)D, pg/mL	4.7 ± 1.2	4.8 ± 1.3	4.7 ± 1.3	.565
1, 25$(OH)_2D_3$, pg/mL	52.4 ± 13.7	52.6 ± 15.4	52.5 ± 14.6	.926

Normally distributed variables are presented as mean ± SD, and non–normally distributed variables are presented as median (IQR).

Abbreviations: BMI, body mass index; IQR, interquartile range.

[a]For continuous data, *P* values are from a Wilcoxon rank-sum test for non–normally distributed variables and a 2 independent-samples *t* test for normally distributed variables. For categorical variables, *P* values are from the Fisher exact test.

[b]Non–normally distributed.

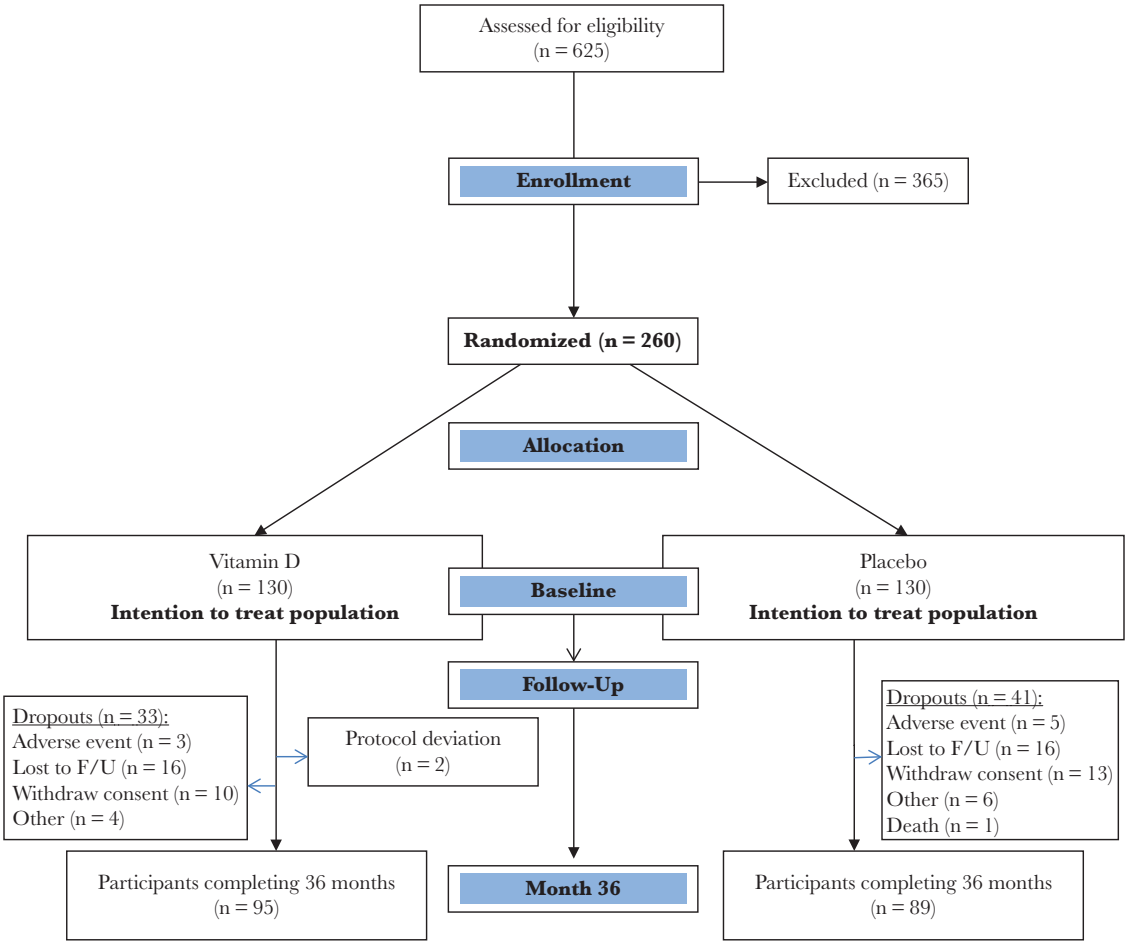

Figure 1. Flow diagram for the study. Two hundred fifteen of the 365 exclusions were due to having a high 25(OH)D level. In both the placebo group and vitamin D group, none of the dropouts were due to a gastrointestinal complaint. One dropout in the vitamin D group represents a subject found to have primary hyperparathyroidism at the 3-month visit. Dropouts designated as "other" were due to relocation out of the state or country, general health issues, and 1 subject who was withdrawn by the principal investigator after having gastric bypass surgery, as this would affect vitamin D absorption.

Efficacy of Treatment on ARI

At 3 months, 24 (21.6%) patients in the vitamin D group reported that they had had an ARI since randomization compared with 25 (21.4%) in the placebo group. At the end of 3 years, both groups reported 18% ARI since their last visit. Overall, the ARI rate did not change significantly from baseline (slope, –0.0081; $P = .232$ for time effect), and it was not different between treatment groups over time (nonsignificant interaction between group and time; slope, 0.00313; $P = .775$) (Figure 2). A Pearson chi-square/degrees of freedom value of 0.81 (close to 1) for our model assures a good fit.

ARI, Vitamin D, and Other Biomarkers

We examined the relationship between ARI and 25OHD3 levels in 2 different ways: (1) using 25OHD levels as a continuous measurement for the entire sample (P value for time and 25(OH)D interaction = .495) and (2) categorizing 25OHD into tertiles (0.3–20.3, 20.3–33.6, and 33.6–73.5 ng/mL). For the tertiles, a model was developed using the categorical tertile indicator and time (P value for the interaction term = .963). In addition, a model was developed for each tertile using time-dependent 25OHD levels (Table 3). Although we observed a larger inverse effect of 25(OH)D3 on ARI in the lower tertile than the other tertiles, it did not reach statistical significance (slope [SE], –0.2826 [0.1496]; $P = .062$). We found no other associations between ARI and 25OHD3 levels over time. Similarly, we evaluated the relationship between ARI and free 25(OH)D and found no association (P value for the time and free 25(OH)D interaction term = .893). The tertile values of free 25(OH)D were (1.5–4.7, 4.7–7.3, and 7.3–23.8 pg/mL).

A subgroup analysis was conducted by restricting the data set to winter months only (December through March). Two separate models were considered to examine the relationships between ARI and vitamin D over time. The first model considered group, time and the 2-way interaction between group and time. The second model considered 25OHD3 levels, time, and the interaction term between 25OHD and time. We found no association between vitamin D supplementation and ARI in either model (P value for the group × time interaction = .831 and for 25OHD × time interaction = .419).

Additionally, we have assessed the relationships of ARI with $1,25(OH)_2D_3$, PTH, serum creatinine, physical activity (caloric expenditure), grip strength, SPPB, and 6-minute walk test, percent body fat, and BMI "over time". None of these factors were associated with ARI in repeated-measures analyses (Table 2).

DISCUSSION

Our findings are similar to those in our previously reported randomized clinical trial (RCT): We found no evidence to support vitamin D supplementation to levels higher than the RDA-associated 25(OH)D level of 20 ng/mL in prevention of ARIs [3]. This is consistent with 8 meta-analyses of the influence of vitamin D on the occurrence of ARIs [23, 36–42] since 2012. Although 3 found a significant positive effect, 5 found no significant effects. Significant heterogeneity was noted between the included trials [21].

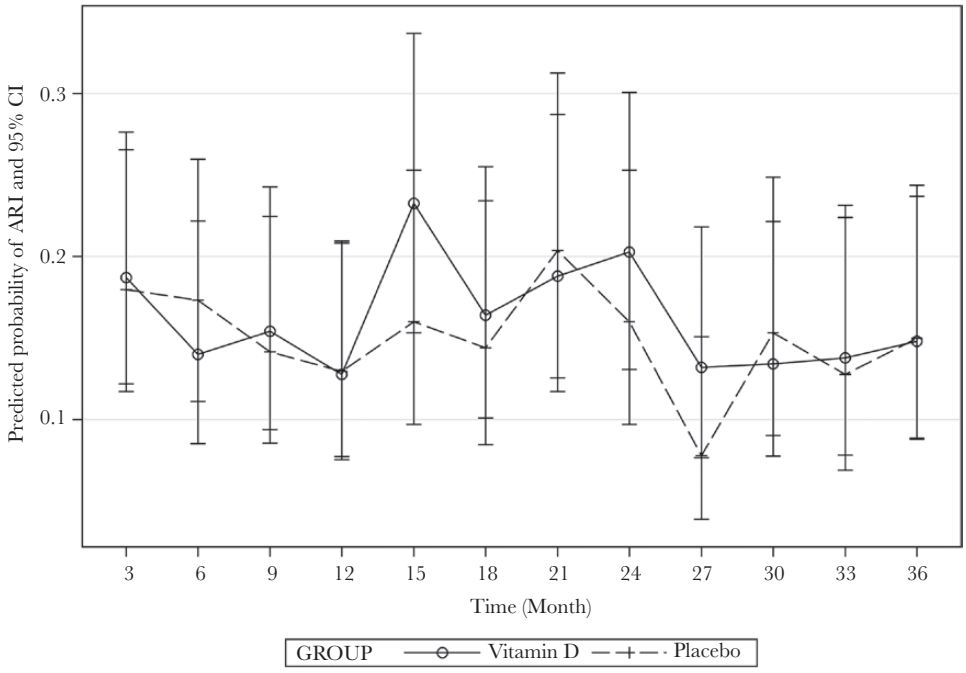

Figure 2. Predicted probability of acute respiratory infections over time estimated by the mixed-effects logistic regression model.

Table 2. Mixed-Effects Logistic Regression Models for ARI Using Vitamin D and Other Biomarkers

Models	Estimate (Standard Error)	*P*
25(OH)D3, ng/mL		
Time, mo	–0.0085 (0.026)	.747
25(OH)D3, ng/mL	–0.0126 (0.020)	.525
Time*25(OH)D3	0.0005 (0.001)	.495
Free25(OH)D, pg/mL		
Time, mo	0.0085 (0.025)	.734
Free25(OH)D, pg/mL	0.0284 (0.073)	.698
Time*Free25(OH)D	–0.0004 (0.003)	.893
1,25(OH)2D3, pg/mL		
Time, mo	0.0110 (0.038)	.771
1,25(OH)2D3, pg/mL	–0.0122 (0.018)	.500
Time*1,25(OH)2D3	–0.0001 (0.001)	.936
PTH, pg/mL		
Time, mo	0.0126 (0.026)	.632
PTH, pg/mL	0.0007 (0.014)	.96
Time*PTH	–0.0001 (0.001)	.807

Abbreviation: ARI, acute respiratory infection.

Most recently, Martineau et al. [43] performed a meta-analysis using individual participant data from 25 randomized controlled trials (10 933 participants). They found a statistically significant reduction from vitamin D supplementation in the risk of having at least 1 ARI. Reasons for heterogeneity between trials were explored by subgroup analyses. There was a strong protective effect in those with 25(OH)D levels <10 ng/mL and no significant effect in those with serum 25(OH)D >10 ng/mL. There was also a protective effect in children (1–16 years old). They also found that whereas daily or weekly doses were protective, bolus doses were not.

In an accompanying editorial, Bolland and Avenell [21] question the significance of these beneficial findings, pointing out that there was only an absolute reduction from 42% to 40% in those having at least 1 acute respiratory infection. Our study was consistent with their conclusion that there is not sufficient evidence at present to recommend vitamin D to prevent ARIs. Whether race is a factor in the prevention of ARIs in the Martineau et al. [43] study could not be ascertained because many studies did not identify race.

Table 3. Regression Models for ARI Using Time-Dependent 25(OH)D3 Values as a Covariate

Models for ARI	[a]Estimate (Standard Error)	*P*
Tertile 1: 25(OH)D3 range 0.3–20.3 ng/mL		
Time, mo	–0.1274 (0.090)	.16
25(OH)D3, ng/mL	–0.2826 (0.1496)	.062
Time*25(OH)D3	0.0102 (0.0063)	.111
Tertile 2: 25(OH)D3 range 20.3–33.6 ng/mL		
Time, mo	–0.2829 (0.1836)	.129
25(OH)D3, ng/mL	–0.1659 (0.1648)	.318
Time*25(OH)D3	0.0105 (0.0067)	.122
Tertile 3: 25(OH)D3 range 33.7–73.5 ng/mL		
Time, mo	–0.0428 (0.0602)	.673
25(OH)D3, ng/mL	–0.0464 (0.0602)	.442
Time*25(OH)D3	0.0012 (0.0022)	.584

Abbreviation: ARI, acute respiratory infection.

[a]Estimates are from mixed-effects logistic regression models.

Our population, with a mean baseline 25(OH)D approximating the RDA, showed no benefit in raising levels to the Endocrine Society Guidelines (20 ng/mL). We have previously reported that we found no benefit of raising 25(OH)D levels >30 ng/mL on bone loss, physical performance, falls, or cognition [28, 29, 31, 43]. We could not find evidence for an effect on ARIs in the current study. However, our patient population may have been too small to detect an effect. Several large studies will soon be reported that may resolve the issue of sample size [44, 45]. Studies in progress, however, may not have sufficient subjects with very low baseline serum 25(OH)D levels. A recent RCT in Vietnamese children found a benefit of vitamin D supplementation in preventing noninfluenza respiratory infection [46].

It has been speculated that total serum 25(OH)D might not indicate a positive effect on ARIs whereas free 25(OH)D might. In the current study, free 25(OH)D was measured using a direct assay. There was no protective effect with either total serum 25(OH)D or free 25(OH)D. In addition, there was no protective effect of serum calcitriol.

We acknowledge several weaknesses in our study. Its findings cannot be extrapolated to men, other racial backgrounds, vitamin D deficiency, other ages and children, or institutionalized individuals. There was no testing for flu or other medically diagnosed influenza-like illness. It is likely that ARI events would have been captured better if real-time techniques were used rather than a 3-month recall. However, faulty recall should apply evenly to both treatment groups, and participants were high functioning. The strengths of our study include using a healthy, community-dwelling population that was studied for 3 years. Serum 25(OH)D was measured using standardized assay methods, and free 25(OH)D was measured as well.

In conclusion, in older healthy black women, we found no difference in self-reported ARIs by maintaining serum 25(OH)D above the current associated RDA value.

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