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The Relationship of Physical Performance and Osteoporosis Prevention with Vitamin D in Older African Americans (PODA)

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Abstract

Rationale—Vitamin D deficiency is associated with bone loss, poor muscle strength, falls and fracture. This information in older African Americans (AAs) is sparse.

Objective—The study of the relationship of Physical performance, Osteoporosis prevention with vitamin D in older African Americans (PODA) is a randomized, double-blind, placebo-controlled 3-year trial examining the effect of vitamin D on bone loss and physical performance in older AA women.

Methods—260 healthy AA women aged >60 years were assigned to receive placebo or vitamin D_3. Initial vitamin D_3 dose was determined by the baseline serum 25OHD level, and adjusted further to maintain serum 25OHD between 30–69 ng/ml. Subjects with baseline 25OHD levels 8 ng/ml or 26 ng/ml were excluded. Objective measures of neuromuscular strength [Short Physical Performance Battery (SPPB), grip strength and 6-minute walking distance (6MWD)] and bone mineral density (BMD) were obtained.

Results—SPPB gait speed, grip strength and 6MWD showed a significant positive correlation with free 25OHD. One pg/ml increase in free 25OHD predicted a 32% increase in the odds of having higher gait speed and a 1.42 lb increase in grip strength. No significant differences in BMI, BMD, muscle mass, grip strength, serum total 25OHD and free 25OHD were observed between groups. None of the measures of physical performance showed an association with baseline serum 25OHD

Conclusions—This is the first study to show an association between free 25OHD and physical performance. These findings indicate a positive relationship of free 25OHD with gait speed and grip strength in older AA women. Further studies are needed to understand the role of free 25OHD.

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1. Introduction

Vitamin D deficiency is prevalent in older adults [1]. The Institute of Medicine determined serum 25OHD 50 nmol/L as adequate for bone health in 97.5% of the population and recommended dietary allowance of vitamin D 600 IU/day for adults aged <70 years and 800 IU/day for those >70 years [2]. The Endocrine Society suggested 25OHD level 75 nmol/L as sufficient and recommend higher vitamin D intake to achieve these levels [3]. Some studies indicate that 25OHD >80 nmol/L is necessary to prevent secondary hyperparathyroidism and related bone loss [4–6], and higher than recommended dose of vitamin D is required to prevent this rise in PTH [7–10]. Ethnic and genetic aspects have not been considered in either recommendations. Despite having lower serum 25OHD than Caucasian Americans (CAs), African Americans (AAs) have higher BMD and fewer fractures [11–13]. Adding to the complexity of this paradox is that 25OHD is not associated with BMD in AAs [13–15]. Strikingly, fracture rates increase with high 25OHD levels [16]. This evidence challenges the use of serum 25OHD as an appropriate biomarker for bone health in AAs.

Recent studies focus on the extraskeletal effects of vitamin D. The AHRQ concluded that evidence supports a link between serum 25OHD and falls [17]. Meta-analyses estimate a 20% reduction in fall risk with vitamin D supplementation in older adults [18]. Emerging evidence also supports the role of vitamin D in physical performance and muscle strength [19–23]. The association between vitamin D deficiency, muscle weakness and poor balance likely underlies the relationship between low serum 25OHD and increased falls. Impaired lower extremity function itself is a major risk factor for frailty and loss of autonomy [24,25]. Age-associated decline in physical performance and concomitant bone loss can increase the risk of falls/fractures. Higher serum 25OHD is associated with greater muscle mass, improved extremity functioning and decreased risk of recurrent falls in older individuals [20,26–29]. Vitamin D may also play a role in chronic conditions that are prevalent with aging and lead to physical a nd functional decline [30,31].

Although an efficient calcium conservation and skeletal resistance to PTH facilitate a higher peak bone mass in AAs [32–34], the skeleton of older AAs is susceptible to the age-associated rise in PTH [35–36]. Bone loss accelerates and bone turnover increases with aging in CAs and AAs. Trials of adequate calcium and vitamin D supplementation have demonstrated a decline in fractures in older CAs by reducing bone loss and falls as a result of improved physical performance [37–43]. The only fracture intervention trial to include older AAs used 400 IU/day of vitamin D, a dose unlikely to achieve the optimal vitamin D status for bone health [44]. Falls occur with same frequency in both populations and fractures are associated with higher mortality and morbidity in AAs [45,46]. In spite of this knowledge, no studies have examined the effect of vitamin D on physical performance and fall prevention in older AAs.

In an exploratory study, we observed an increase in muscle strength and a reduction in bone turnover markers with vitamin D_3 supplementation [47]. We hypothesized that vitamin D supplementation will reduce bone loss and improve physical performance in older AAs. Hence, we performed a randomized, double-blind, placebo-controlled vitamin D_3 trial in older AA women. Here, we describe the baseline findings of this trial.

2. Study Design and Methods

2.1. Study Population

The Physical Performance, Osteoporosis Prevention and Vitamin D in older African Americans (PODA) Study is a prospective, randomized, double-blind, placebo controlled, three-year clinical trial of vitamin D_3 supplementation in postmenopausal AA women older than 60 years of age. The trial was approved by the Institutional Review Board of Winthrop University Hospital. Ambulatory volunteers were recruited from Long Island and surrounding communities. African American ancestry of the participants was assessed by self-declaration that both parents and at least 3 of 4 grandparents were African American. Participants with 25OHD 8 ng/ml (20 nmol/L) and 26 ng/ml (65 nmol/L) at baseline were excluded from the study. Exclusion criteria also included metabolic bone disease, BMD at total hip below 2.5 standard deviation {using female reference ranges from the dual-energy x-ray absorptiometer (DXA) manufacturer}, history of osteoporotic fracture, previous treatment with bone active agents and any medication or chronic illness that affects bone metabolism, calcium or parathyroid disorder, and use of medications known to interfere with vitamin D metabolism.

ClinicalTrials.gov—The trial is registered at www.ClinicalTrials.gov as NCT01153568.

2.2. Study Design

Randomization of 260 healthy participants to vitamin D_3 or placebo group was done through a computer-generated sequence. One-half of the subjects were randomly assigned to active vitamin D_3 (n=130) and the other one-half to matching placebo (n=130). Treatment assignments in labeled sealed envelopes were provided to the research pharmacist by the study statistician. Subjects and investigators were blinded. Initial vitamin D_3 dose was determined by a research pharmacist depending on the baseline serum 25OHD levels [investigators and participants were blinded]. If baseline 25OHD was 8–10 ng/ml (20–25 nmol/L), participants were assigned 120 μg (4800 IU) daily dose; 90 μg (3600 IU) daily if baseline 25OHD was 10–20 ng/ml (25–50 nmol/L); or 60 μg (2400 IU) daily if baseline 25OHD was 20–26 ng/ml (50–65 nmol/L). The vitamin D_3 dose was adjusted further at 3-month intervals to maintain the serum 25OHD level between 30–69 ng/ml (75–172 nmol/L). The blind was maintained by adjusting the placebo dose to match the distribution of dose changes in the active group (a double-dummy design).

2.3. Study Procedures

Objective measures of anthropometric, neuromuscular function, strength, and qualitative variables were obtained at baseline and 3-month intervals. Daily calcium intake was assessed by a food frequency questionnaire (Short Calcium Questionnaire 2002; NIH

Clinical Center). Calcium supplements, as calcium carbonate were provided to both the active and control group to ensure a total calcium intake of at least 1200 mg daily in divided doses with meals. Methods used for participant recruitment and retention in the study assisted in ensuring compliance with the study visits and procedures.

Information from study participants was obtained through several different means including a self-administered questionnaire, interviewer-administered questionnaire, and clinic examination. Numerous baseline assessments were made in order to have a comprehensive set of variables from study participants to relate to osteoporotic fracture risk in women or to the sequelae of fracture. These measurements are described in detail below and a comprehensive list of the individual measures obtained at baseline are provided in Table 1.

2.4. Outcome Measures

The primary goal of this study is to quantify the contribution of vitamin D_3 on physical performance and BMD changes in older AA women. An additional outcome is the incidence of falls and fractures in response to vitamin D_3.

Skeletal Measures—Bone mineral density measurement was performed at 6 month intervals at the total hip, non-dominant midradius, and anteroposterior spine with a DXA (model QDR 4500, version 9.80D; Hologic Inc., Waltham, Massachusetts).

Anthropometric Measures—All measures were taken at baseline by an examiner using standard equipment, including a Harpenden stadiometer and a digital Seca scale. Additional physical measures included pulse and seated blood pressure at the arm.

Physical Performance and Measures of Strength—Neuromuscular function was assessed by the Short Physical Performance Battery (SPPB), grip strength and 6-minute walking distance (6MWD) at baseline and every 6 months thereafter.

  – The SPPB, developed by the National Institute on Aging for the Established Populations for Epidemiologic Studies of the Elderly was used to assess lower extremity physical performance [48–50]. SPPB consists of hierarchical balance tests (side-by-side, semi-tandem, tandem and single leg stands for 10 seconds each), two timed 4-meter walks to assess usual gait speed, and a chair stand test (timed 5 rises). Performance scores for each test and a summary score aggregating these assessments were calculated as per standard SPPB protocol. Each of the SPPB components has a maximum score of 4 points (total SPPB maximum score being 12), with higher scores indicative of better lower extremity performance. In this study, the Hawaii modification of the SPPB was administered. The Hawaii modification expands the original SPPB battery to make it more demanding to avoid a "ceiling effect." In addition to producing its own score, the modified battery also allows for the calculation of a score for the traditional SPPB. Under this modification participants completed 10 repeated chair stand rises.

  – Grip strength, an indicator of upper extremity muscle strength, was measured using a handgrip dynamometer (Jamar Dynamometer; Alimed Inc., Dedham, Massachusetts). Grip strength was measured in the dominant hand and the mean of

three measurements was recorded. The outcome was force generated (lb/in^2), with higher values indicative of greater grip strength.

– Participants also completed a 6-minute walk (6MWD) to assess walking endurance. The outcome was total distance traveled in meters. The mean distance covered in six minutes of walking by healthy older adults is > 500 meters [51].

Lifestyle, medical, and nutritional factors—To examine the association between fracture risk and lifestyle and medical characteristics, numerous aspects of personal and medical history were assessed at baseline. Information obtained by self-administered questionnaire included level of education and marital status, medical history, medications, diet history, physical activity, fall and fracture history, tobacco use and alcohol consumption. Participants brought current prescription medications to each visit and the names and doses of all medications were recorded. Physical activity expenditure was assessed from the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire [52]. Additional information on alcohol intake and physical activity was obtained using an interviewer-administered questionnaire. Alcohol intake was quantified in terms of usual drinks per day.

2.5. Laboratory Tests

Fasting blood samples were collected at baseline and at 3 monthly visits. Serum samples for measurement of 25OHD and vitamin D metabolites [25(OH)D$_2$, 25(OH)D$_3$, 24,25(OH)$_2$D$_3$, 1,25(OH)$_2$D$_2$, and 1,25(OH)D$_3$] were analyzed by the Department of Laboratory Medicine at the University of Washington (Seattle, Washington) using liquid chromatography-tandem mass spectrometry with deuterated internal standards for each analyte [53]. Concentrations of 25(OH)D$_2$, 25(OH)D$_3$, and 24,25(OH)$_2$D$_3$ were standardized to NIST SRM 972a [54]. The % CV of these assays in the specific ranges are as follows: 1,25(OH)D$_3$: 7.95–10.40% CV at 18.1–47.8 pg/mL; 25(OH)D$_3$: 3.54–4.41%CV at 9.5–32.3 ng/mL; 24,25(OH)$_2$D$_3$: 5.17–7.42%CV at 1.3–4.6 ng/mL.

Serum free 25OHD was directly measured using ELISA based on a two-step immunoassay procedure (Future Diagnostics, Wijchen, The Netherlands) as previously described [55,56]. Markers of bone turnover and parathyroid hormone 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, California, inter-assay CV: 1.34%). Serum Bone alkaline phosphatase and serum C-Telopeptide of Type-1 collagen were measured by a one-step enzyme-linked immuno-absorbent assay (Micro Vue BAP, Quidel Corp., San Diego, California and Nordic Bioscience Diagnostics, Herlev, Denmark). The intra-assay CV of the bone alkaline phosphatase assay is 4–6% and the inter-assay CV is 5–8%. The intra-assay CV of the CrossLap assay is 5.4%, and the inter-assay CV is 6.5%. Serum and urinary calcium were measured by O-cresolphthalein complex using automated equipment (Dimension-RXL, Dade, Delaware).

2.6. Data and Participant Safety

Study design, recruitment strategies, compliance, and data and participant safety were monitored semi-annually by a Data Safety and Monitoring Board appointed by the NIH.

Safety measures including a serum chemistry panel were performed at baseline and at each randomization visit. Most data and specimens were collated for later analysis. Participants were informed of the abnormal results of any available assessments. Women who had BMD measures that were unequivocally low (T score less than 2.5, using female reference ranges from the DXA manufacturer) were referred to their physician. In general, participants continued to receive their routine medical care during the study period.

2.7. Statistical Analysis

Block randomization was performed at baseline using a computer generated (SAS Proc Plan) randomization list. Subjects were assigned to one of the two groups: vitamin D_3 supplementation or placebo. Descriptive statistics (i.e. mean, median, standard deviation, first quartile and third quartile) were generated and presented as mean ($\pm$SD) or median (q1–q3) as appropriate for continuous data and as proportion for categorical variables. Normality of distributions of clinical variables and laboratory markers was evaluated using visual observation of histograms and the Kolmogorov-Smirnov test. Differences of each continuous variable between groups were examined using the non-parametric Wilcoxon rank-sum test for non-normally distributed and two independent samples t-test for normally distributed variables. Variables were checked for outliers using Horn's method using 'Reference Intervals' package in R. Analyses were performed with and without outliers but output remained similar, so full data were used. Fisher's exact test was used to compare categorical variables between groups.

The relationships of clinical and demographics variables with serum free 25OHD and 25OHD$_3$ were examined using Pearson and Spearman correlation coefficients as appropriate. Scattered plots of continuous variables with non-parametric smoothed curve (LOESS) and linear regression lines as appropriate were used to evaluate degree and nature of the particular relationships. We presented the final figure using linear regression as the LOESS did not look different.

SPPB gait speed score ranged from 1 through 4. Only one patient had a score of 1 and was excluded for this analysis. We would need at least 10 observations for each category of dependent variable to fit a valid model [57]. A cumulative logistic regression model was developed using free 25OHD as the independent variable. Score test was used to evaluate the proportional odds assumptions. AIC and log likelihood criteria were used to test the model fit. Linear regression model was developed for grip strength using free 25OHD as the independent variable. Model assumptions were checked via residual analysis and graphic summaries.

Multivariable models for both gait speed score and grip strength were examined in order to adjust for potential confounders. Both models considered age, BMI, free 25(OH)D, 25(OH)D$_3$, 1,25(OH)$_2$D$_3$, PTH, and serum creatinine as the plausible predictors. In order to arrive at the final cumulative logistic regression model presented, AIC, log likelihood criteria and c-statistic were examined. For the final multiple linear regression model reported, an exhaustive search of the model space was conducted and models were ranked on the basis of their adjusted R^2 values. Due to likely co-linearity between different

variables, the final models presented were considered representative of other equally informative models.

All calculations were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA) and R (http://www.Rproject.org). Results were considered statistically significant when P < 0.05.

3. Results

3.1. Comparisons of Baseline Characteristics

Selected baseline characteristics of the study population are presented in Table 1. The average age was 68.2 (65.4–72.5) years. Body mass index was similar between groups [overall 30 (26.5–34.1) kg/m^2]. Most rated their health as good/excellent. Few were current smokers, although 21.5% in the active group and 23.8% in the placebo group had smoked previously. 43.1% in the active group and 34.6% in the placebo group reported no alcohol intake, while 55.4% and 63.9%, respectively, consumed at least 2 drinks per week. In the overall sample, no statistically significant relationship was detected between serum total 25OHD concentration and BMI, calcium intake, BMD, muscle mass, percent body fat or measures of physical performance (SPPB balance, gait speed, chair stand score, SPPB total score, grip strength or 6MWD).

Median daily calcium intake including supplements was 842 (600-1142) mg/d in the vitamin D$_3$ group and 827 (628-1185) mg/d in the placebo group. There were no significant differences in the mean BMD, muscle mass and percent body fat between the active and control group. The mean SPPB balance and gait speed, 10 chair stands time and grip strength were also similar in both groups. Participants randomized to the vitamin D$_3$ group had a somewhat higher physical performance at baseline (as assessed by the mean SPPB total score and 6MWD) compared to the subjects in the placebo group [12 (10–12) vs. 11 (10–12), P = 0.009 and 407 (357 – 453) vs. 387 (324 – 432), P = 0.015 respectively].

There were no significant differences in the mean values of serum total 25OHD (21.5 ± 6.5 ng/l and 22.2 ± 6.9 ng/l) and free 25OHD (4.7 ± 1.2 pg/ml and 4.8 ± 1.3 pg/ml respectively) between groups of subjects. Between group PTH levels also showed no significant differences. In addition, the serum calcium, phosphorus and creatinine concentrations were normal.

3.2. Overall association between clinical outcomes and baseline characteristics

SPPB Gait speed score—Free 25OHD significantly predicted [OR (95% CI) =1.32(1.06–1.63), p=0.012] gait speed score in a cumulative logistic regression model. This suggests 32% increase in the odds of having higher gait speed score for one pg/ml increase in free 25OHD. This model was further adjusted for age, BMI, free 25OHD, 25(OH)D$_3$, 1,25(OH)2D$_3$, PTH, and serum creatinine. Free 25OHD [adjusted OR=1.28(0.90–1.82)] did not predict gait speed in the adjusted model. The final model after an exhaustive model search based on AIC and log likelihood criteria included age [OR=0.91(0.86–0.95)] and BMI [OR=0.93(0.89–0.97)].

Grip Strength—Free 25OHD significantly predicted grip strength in a linear regression model (R-Square=0.02, F=5.22, regression coefficient [β] = 1.52, p=0.023) suggesting 1.52 lb increase in grip strength for one pg/ml increase in free 25OHD. Adjusted multivariable model considered age, BMI, free 25(OH)D, 25(OH)D$_3$, 1,25(OH)$_2$D$_3$, PTH, and serum creatinine as the potential explanatory variables. After an exhaustive model search based on R-square values, the final model (R-Square=0.12, F=11.21, p<.0001) included age (β= −0.69, p<.0001), BMI (β =0.30, p=0.023), and Free 25OHD (β=1.42, p=0.031) as the independent predictors of grip strength. Adjusted for age and BMI, one pg/ml increase in free 25OHD increases grip strength by 1.42 lb. Figure 1 depicts relationship between grip strength and free 25OHD. Serum total 25OHD concentration did not relate to grip strength.

4. Discussion

This is the first study to show an association between free 25OHD and physical performance. In this first report from the PODA Study, we found a significant positive relationship of free 25OHD with the SPPB gait speed, grip strength and 6MWD at baseline. An increase in free 25OHD predicted an increase in grip strength (after adjusting for age and BMI) and in the odds of having higher gait speed score (in an age adjusted model). None of the measures of physical performance (SPPB gait speed, SPPB total score, 10 chair stand time, grip strength and 6MWD) or muscle mass were influenced by the baseline total 25OHD in the overall cohort analysis or in the two randomization groups. This is in concordance with previous studies in other populations [58–60]. Studies that reported a positive association between total 25OHD and physical performance in older adults also included individuals deficient in vitamin D, unlike our study population [20,59–62].

We noted an inverse correlation between BMI and free 25OHD. This could be due to the higher vitamin D binding protein (VDBP) concentrations reported in higher weight individuals compared to normal-weight individuals and hence the lower free hormone concentration. VDBP coding gene polymorphisms may also play a role in VDBP concentrations at higher body weights [63,64]. However, we used a direct measurement of free 25OHD, a more accurate method compared to the calculated measurement based on VDBP. We previously confirmed that total 25OHD measurements may not precisely reflect biological activity in AAs [65]. In this study, we noted no relationship between total 25OHD and BMI. It is possible that free 25OHD is a stronger biomarker than total 25OHD.

Any new proposed biomarker for vitamin D status must not only reflect vitamin D exposure but also be related to outcomes such as calcium absorption, PTH levels, BMD, fracture, falls, physical performance or muscle strength. The literature on free 25OHD and functional markers of vitamin D status has emerged in the recent years and is inconclusive thus far, except for the associations with PTH. In our previous studies, we found no advantage of measuring free 25OHD over total 25OHD both at baseline and in response to vitamin D intake. We also found no advantage of measuring free over total 25OHD in assessing the response of calcium absorption, PTH and bone turnover markers [56]. In this study, we noted an inverse relationship of PTH with both total and free 25OHD, but there was no association between BMD and total or free 25OHD levels. This is in agreement with the findings of our previous study in AAs [13–15]. Other studies have also found no correlations

between BMD and total and bioavailable 25OHD concentrations in AAs, whereas a positive correlation was noted in CAs [66,67].

In contrast to clinical studies, preclinical data are more consistent. In a study comparing mice ingesting vitamin D_2 to mice ingesting vitamin D_3, the total 25OHD levels were comparable, but the free 25OHD level [all $25OHD_2$] was higher in the mice on vitamin D_2 due to the lower affinity of VDBP for $25OHD_2$ [68]. Free 25OHD was associated with increased bone volume density and increased numbers of osteoclasts and osteoblasts in the mice on the vitamin D_2, suggesting that free 25OHD level may be a better indicator than total 25OHD for the effects of vitamin D on bone metabolism.

Physical performance is the result of many factors affecting muscle mass and strength over the life span. Notwithstanding the high reliability of the assay we used for direct measurement of free 25OHD, measured 25OHD levels (free or total) are subject to fluctuations due to various dynamic indices including recent sun exposure, diet, gastrointestinal disease, and the quality of antibody used to bind the free 25OHD. It is possible that our observation of association of free 25OHD and physical performance is a random finding. However, free 25OHD was related to both measures of lower extremity strength (gait speed and 6MWD) and one measure of upper extremity strength (grip strength). Studies suggest a direct effect of vitamin D on muscle function [22,23]. A plausible mechanism underlying the association of free 25OHD and physical performance is that vitamin D maintains muscle integrity in older adults by preventing intramuscular fat accumulation [69]. Vitamin D exerts its effect on muscle via VDRs [22,23]. Therefore, it can be postulated that higher concentration of bioavailable (free) 25OHD results in upregulation of VDR in skeletal muscle and increases transportation of calcium and phosphorus into muscle cells [70]. Similarly, high free 25OHD may also promote de novo protein synthesis in muscle, particularly of type II fibers, an established effect of calcitriol in studies in older adults [71,72].

Impaired muscle function may even precede the appearance of biochemical signs of bone disease during vitamin D deficiency [19]. A decline in physical performance combined with age related bone loss can lead to an increase in the incidence of falls and fractures in older adults. Higher serum 25OHD concentrations have been associated with lower risk of falls in older adults [17,18]. Cross-sectional studies suggest positive association between serum 25OHD and physical performance and strength among older adults [21,27,62] while data from longitudinal studies are conflicted. Some studies showed no relationship and other studies noted greater declines in physical performance with vitamin D deficiency [20,37–43,58,61,73]. Further studies are needed to understand the role of free 25OHD in physical performance in older adults.

Although AAs have lower serum 25OHD than CAs, older AAs are underrepresented in the studies investigating extraskeletal benefits of vitamin D. The focus of Institute of Medicine 2010 recommendations was the healthy population rather than disease related conditions and evidence was found to be insufficient to recommend intake for outcomes beyond bone health. Whether serum 25OHD concentration 50 nmol/L, deemed as adequate by the Institute of Medicine, or serum 25OHD concentration 75 nmol/L, proposed as optimal by

the Endocrine Society, is effective in achieving extraskeletal benefits of vitamin D in this population is also unknown. The PODA trial is designed to examine these associations in older healthy vitamin D sufficient AA women.

Our study has strengths and some limitations. This randomized trial includes a placebo control group. We took into consideration covariables that are known confounders (age, BMI). In older individuals, other variables, such as chronic diseases, may influence the measured outcomes other than serum 25OHD. Our study cohort includes relatively healthy participants. Results from this study may not be extrapolated to men, women of other ethnic groups or to those with chronic conditions. Our study population is vitamin D sufficient according to the serum 25OHD concentration 50 nmol/L recommended by the Institute of Medicine. We also ensured adequate daily calcium intake. Due to the absence of confounding from hypovitaminosis D at baseline, this population represents an ideal cohort to study the effect of higher serum 25OHD concentrations on physical performance and falls in older healthy African American population.

5. Conclusion

Baseline findings of the PODA Study suggest the usefulness of free 25OHD as a predictor of physical performance in aging African American women. Although this finding could be a random finding, the association of free 25OHD with measures of both upper and lower extremity performance lends support to further examination of the role of serum free 25OHD in physical performance to prevent frailty and fracture in older adults. Longitudinal dose response studies that use standardized, reproducible assessments of physical performance and muscle strength are needed to define target serum 25OHD level and optimal vitamin D intake for extraskeletal outcomes.

Acknowledgments

Abbreviations

1,25OHD	1,25-dihydroxyvitamin D
25OHD	25-hydroxyvitamin D
BMD	bone mineral density
BMI	Body Mass Index
DXA	Dual-energy X-ray Absorptiometry
VDBP	Vitamin D Binding Protein
IU	international units
PTH	parathyroid hormone

| **SPPB** | Short Physical Performance Battery |

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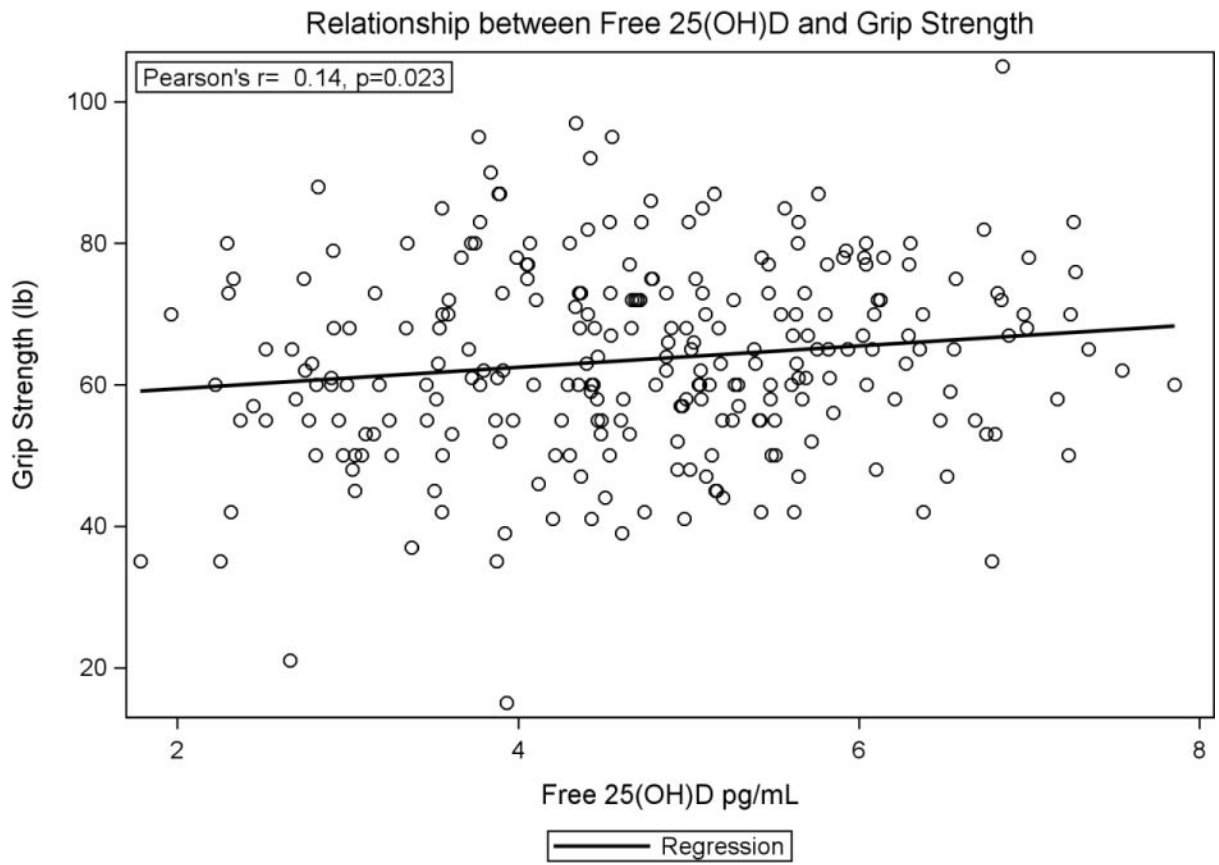
Figure 1.
Relationship between Free 25OHD and Grip Strength

Table 1

Demographics and Baseline Characteristics

	Active (N=130)	Placebo (N=130)	Overall (N=260)	P-value[1]
Demographics and behavioral				
Age (years) [†]	67.8 (65.1 – 71.5)	69.0 (65.4 – 73.4)	68.2 (65.4 – 72.5)	0.251
BMI (kg/m^2) [†]	30.2 (26.4 – 34.6)	30.0 (26.8 – 33.9)	30.1 (26.6 – 34.1)	0.867
Calcium intake (mg) [†]	842.0 (600 – 1142)	826.5 (628.0 – 1185)	828.0 (614.0 – 1164)	0.857
Smoking History, n (%)				0.805
Present	7(5.4)	5(3.9)	12 (4.6)	
Past	28 (21.5)	31 (23.8)	59 (22.7)	
Never	95 (73.1)	94 (72.3)	189 (72.7)	
Alcohol History, n (%)				0.323
Present	72 (55.4)	83 (63.9)	155 (59.6)	
Past	2 (1.5)	2 (1.5)	4 (1.5)	
Never	56 (43.1)	45 (34.6)	101 (38.9)	
Physical Performance and Activity				
SPPB Balance Score [†]	4 (4 – 4)	4 (4 – 4)	4 (4 – 4)	0.948
SPPB Gait Speed Score [†]	4 (3 – 4)	4 (3 – 4)	4 (3 – 4)	0.312
SPPB 5 Chair Stand Score [†]	4 (3 – 4)	3 (2 – 4)	4 (3 – 4)	0.002
SPPB Total Score [†]	12 (10 – 12)	11 (10 – 12)	11 (10 – 12)	0.009
10 Chair stand time (seconds) [†]	23.0 (18.6 – 27.7)	24.2 (19.4 – 28.5)	23.5 (19.1 – 28.2)	0.191
Grip Strength (lb/in^2)	64.7 ± 13.4	61.9 ± 13.9	63.3 ± 13.7	0.100
Caloric expenditure/week, kcal/wk [†]	3637 (2352 – 5166)	3092 (1912 – 4908)	3392 (2064 – 4963)	0.202
6-minute walking distance (meters) [†]	407.0 (357.0 – 453.0)	387.0 (324.0 – 432.0)	396.0 (347.0 – 444.0)	0.015
Bone Density				
Hip total BMD (g/cm^2)	0.919 ± 0.130	0.935 ± 0.134	0.927 ± 0.132	0.329
T-score total femur	−0.185 ± 1.065	−0.054 ± 1.096	−0.120 ± 1.080	0.329
Femoral neck BMD (g/cm^2) [†]	0.767 (0.694 – 0.9)	0.805 (0.718 – 0.9)	0.785 (0.707 – 0.9)	0.109
Wrist 1/3 BMD (g/cm^2)	0.689 ± 0.067	0.692 ± 0.075	0.691 ± 0.071	0.684
Spine BMD (g/cm^2)	1.005 ± 0.162	1.023 ± 0.171	1.014 ± 0.167	0.396
Whole body total BMD (g/cm^2) [†]	1.127 (1.076 – 1.2)	1.156 (1.070 – 1.2)	1.138 (1.070 – 1.2)	0.222
Whole body muscle mass (g) [†]	44885 (40629 – 50305)	44129 (40412 – 49323)	44549 (40546 – 49560)	0.502
Arms muscle mass (g) [†]	4544 (4132 – 5173)	4304 (3854 – 4953)	4435 (3970 – 5071)	0.063
Legs muscle mass (g) [†]	14700 (13278 – 16733)	14860 (13167 – 16752)	14821 (13208 – 16752)	0.860
Append. Muscle Mass/Height^2 (kg/m^2) [†]	7.8 (7.1 – 8.5)	7.7 (7.2 – 8.4)	7.8 (7.1 – 8.5)	0.696
Total percent body fat	40.4 ± 5.0	41.3 ± 5.0	40.8 ± 5.0	0.151

	Active (N=130)	Placebo (N=130)	Overall (N=260)	P-value[1]
Laboratory				
Free 25OH Vitamin D (pg/ml)	4.7 ± 1.2	4.8 ± 1.3	4.7 ± 1.3	0.565
25(OH)D$_3$, ng/ml	21.5 ± 6.5	22.2 ± 6.9	21.8 ± 6.7	0.352
1,25(OH)$_2$D$_3$, pg/ml	52.4 ± 13.7	52.6 ± 15.4	52.5 ± 14.6	0.926
24,25(OH)$_2$D$_3$, ng/ml	1.4 ± 0.6	1.5 ± 0.7	1.4 ± 0.6	0.107
PTH (pg/ml)[†]	56.1 (41.0 – 73.6)	56.4 (39.5 – 73.8)	56.2 (39.8 – 73.8)	0.977
Serum Ca (mg/dl)[†]	9.5 (9.3 – 9.8)	9.5 (9.3 – 9.8)	9.5 (9.3 – 9.8)	0.943
Serum Cr (mg/dl)[†]	0.8 (0.7 – 0.9)	0.7 (0.6 – 0.9)	0.8 (0.6 – 0.9)	0.472
Serum P (mg/dl)[†]	3.5 (3.2 – 3.8)	3.5 (3.2 – 3.8)	3.5 (3.2 – 3.8)	0.732

[1] For continuous data, p-values are from Wilcoxon rank-sum test for non-normally distributed variables and two independent samples t-test for normally distributed variables. For categorical variables, p-values are from Fisher's exact test.

[†] Not normally distributed; IQR=Inter-quartile range (first quartile – third quartile); SD=Standard Deviation; Normally distributed variables were presented as mean ±SD and not normally distributed variables were presented as median (IQR).

Table 2

Correlations with Free 25OHD and Total 25OHD$_3$

Variable	Free 25(OH)D pg/ml		25OHD$_3$ ng/ml	
	Rho	**P value**	**Rho**	**P value**
Age (years)[†]	−0.16	0.009	0.12	0.052
BMI (kg/m^2)[†]	−0.17	0.006	−0.03	0.679
Calcium intake (mg)[†]	0.08	0.229	0.03	0.585
SPPB Balance Score[†]	0.03	0.634	−0.05	0.463
SPPB Gait Speed Score[†]	0.16	0.009	0.02	0.751
SPPB 5 Chair Stand Score[†]	0.01	0.814	−0.04	0.477
SPPB Total Score[†]	0.08	0.177	−0.04	0.556
Grip Strength (lb/in^2)	0.14	0.023	0.05	0.441
10 Chair stand time[†]	−0.06	0.365	0.02	0.693
6-minute walking distance (meters)[†]	0.14	0.026	0.02	0.725
Caloric expenditure/week, kcal/wk[†]	0.06	0.357	0.04	0.522
Hip total BMD (g/cm^2)	−0.04	0.549	0.02	0.799
T-Score total femur	−0.04	0.549	0.02	0.799
Femoral neck BMD (g/cm^2)[†]	0.01	0.904	0.02	0.781
Wrist 1/3 BMD (g/cm^2)	−0.03	0.685	−0.07	0.263
Spine BMD (g/cm^2)	−0.10	0.105	−0.08	0.196
Whole body total BMD (g/cm^2)[†]	−0.01	0.890	−0.09	0.169
Whole body muscle mass (g)[†]	−0.05	0.421	−0.05	0.402
Arms muscle mass (g)[†]	−0.06	0.326	−0.06	0.321
Legs muscle mass (g)[†]	−0.05	0.454	−0.08	0.217
Append. Muscle Mass/Height^2 (kg/m^2)[†]	−0.10	0.129	−0.08	0.231
Total percent body fat	−0.09	0.134	0.04	0.541
Free 25OH Vitamin D (pg/ml)	1.00		0.65	<.0001
25(OH)D$_3$, ng/ml	0.65	<.0001	1.00	
1,25(OH)$_2$D$_3$, pg/ml	−0.06	0.313	0.15	0.016
24,25(OH)$_2$D$_3$, ng/ml	0.72	<.0001	0.80	<.0001
PTH (pg/ml)[†]	−0.13	0.043	−0.16	0.013
Serum Ca (mg/dl)[†]	0.04	0.505	0.10	0.106
Serum Cr (mg/dl)[†]	0.08	0.176	0.08	0.216
Serum P (mg/dl)[†]	−0.09	0.156	0.00	0.964

[1] P-values and rhos are reported from Spearman Correlation Coefficients analysis for non-normally distributed variables and Pearson for normally distributed variables.

†Not normally distributed