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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 and 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. 1 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.

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

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; IU, international units; PTH, parathyroid hormone; SPPB, Short Physical Performance Battery; VDBP, Vitamin D Binding Protein

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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 and 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 $\leq$ 8 ng/ml (20 nmol/L) and $\geq$ 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 and 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 every 6-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.

2.4.1. 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).

2.4.2. 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.

2.4.3. 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.