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Physical activity, sedentary behavior, and vitamin D metabolites

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ABSTRACT

Physical activity is associated with circulating 25-hydroxyvitamin D (25(OH)D). However, the influence of activity and/or sedentary behavior on the biologically active, seco-steroid hormone 1α,25-dihydroxyvitamin D (1,25(OH)$_2$D) is unknown. We conducted a cross-sectional analysis among ursodeoxycholic acid (UDCA) randomized trial participants ($n = 876$) to evaluate associations between physical activity, sedentary behavior, and circulating vitamin D metabolite concentrations. Continuous vitamin D metabolite measurements and clinical thresholds were evaluated using multiple linear and logistic regression models, mutually adjusted for either 1,25(OH)$_2$D or 25(OH)D and additional confounding factors. A statistically significant linear association between 1,25(OH)$_2$D and moderate-vigorous physical activity per week was strongest among women (β (95% CI): 3.10 (1.51–6.35)) versus men (β (95% CI): 1.35 (0.79–2.29)) in the highest tertile of activity compared to the lowest (p-interaction = 0.003). Furthermore, 25(OH)D was 1.54 ng/ml (95% CI 1.09-1.98) higher per hour increase in moderate-vigorous activity ($p = 0.001$) and odds of sufficient 25(OH)D status was higher among physically active participants ($p = 0.001$). Sedentary behavior was not significantly associated with either metabolite in linear regression models, nor was a statistically significant interaction by sex identified. The current study identified novel associations between physical activity and serum 1,25(OH)$_2$D levels, adjusted for 25(OH)D concentrations. These results identify the biologically active form of vitamin D as a potential physiologic mechanism related to observed population-level associations between moderate-vigorous physical activity with bone health and chronic disease risk. However, future longitudinal studies are needed to further evaluate the role of physical activity and vitamin D metabolites in chronic disease prevention.

1. Introduction

Low physical activity levels, and more recently high levels of sedentary behavior, are associated with increased risk of common diseases including cardiovascular disease, diabetes, and cancer [1–6]. Furthermore, the evidence for a role of sedentary behavior, independent of physical activity, in chronic disease etiology is growing, but equivocal [7–10]. Hypotheses suggested for the underlying biological mechanism of action for higher physical activity and lower sedentary behavior in disease etiology include reduced inflammation, increased insulin sensitivity, and epigenetic modifications of genes [11–14]. However, the relationship with vitamin D metabolites is not well understood. Previous studies demonstrate that physical activity is associated with higher 25-hydroxyvitamin D (25(OH)D) levels [15–17], though to date, only a single small study has evaluated the biologically active form of vitamin D, the seco-steroid hormone 1α,25-hydroxyvitamin D (1,25(OH)$_2$D), and none the role of overall sedentary behavior. Thus, it is not known if physical activity or sedentary behaviors act to influence vitamin D metabolite concentrations independently or in combination.

Research has established that vitamin D is essential to human health [18–21]. Low vitamin D status, which is commonly evaluated through 25(OH)D levels, is associated with increased risk of several diseases [21–26]. A variety of factors are related to 25(OH)D concentration [15,16,27] and previous studies evaluating predictive models for circulating 25(OH)D have consistently identified physical activity as an important factor [15–17], though total sedentary behavior has not been evaluated. In contrast, previous studies also propose that activity level is not associated with 1,25(OH)$_2$D, since it is hypothesized that concentrations are maintained within a narrow range due to its central role in calcium homeostasis [18,28]. Yet, other studies demonstrate that circulating 1,25(OH)$_2$D levels may be associated with disease risk [26,29], and also related to physical activity [30]. However, researchers and practitioners debate the clinical thresholds for optimal 25(OH)D status [31,32] and 1,25(OH)$_2$D is not commonly measured clinically.

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Furthermore, no identified studies have evaluated the independent associations between physical activity and total sedentary behavior with 25(OH)D or $1,25(OH)_2D$ levels in adults.

In the present study, we hypothesized that high physical activity is associated with increased $1,25(OH)_2D$ and 25(OH)D concentrations, and that sedentary behavior is associated with lower 25(OH)D. Furthermore, we hypothesized that high physical activity is associated with higher odds of clinically optimal vitamin D levels. In order to evaluate the independent role of activity versus sedentary behavior in vitamin D metabolite levels, we conducted the first study to mutually adjust all physical activity models for sedentary behavior, $1,25(OH)_2D$ models for 25(OH)D, as well as the reverse in each case. The results from this study will improve our understanding of the relationship between physical activity and sedentary behavior in circulating vitamin D metabolite levels, and inform future studies evaluating chronic disease prevention.

2. Methods

2.1. Study population

The ursodeoxycholic acid (UDCA) trial was a randomized, double blind, placebo-controlled phase III trial to evaluate the influence of UDCA on colorectal adenoma recurrence conducted at the University of Arizona, which has been described in detail previously [33]. Participants included Arizona residents from 40 to 80 years of age with at least one colorectal adenoma (>3 mm in diameter) removed within 6 months of study enrollment. Participants were recruited between 1999 and 2000 and were followed for approximately 3 years [33,34]. The present study included all participants with complete data for circulating vitamin D metabolite concentrations and activity levels ($n = 876$) at the baseline visit. This University of Arizona Human Subjects committee approved this trial.

2.2. Assessment of physical activity, sedentary behavior, and vitamin D metabolites

Non-occupational physical activity and sedentary behavior were measured at baseline using the Arizona Activity Frequency Questionnaire (AAFQ), a validated instrument that measures 59 activities with indicators of frequency and duration during the prior month [35]. "Sedentary behavior" was classified as behaviors ≤1.5 METs, "light" between 1.5 METs and 3 METs, and "moderate-vigorous" ≥ 3 METs per physical activity [36,37]. In order to reduce bias introduced by measurement error, the reported time in each activity was proportionally adjusted to allow for the duration of all reported activities plus sleep to total 24 h [38]. Examples of the activities evaluated by the AAFQ have been described previously [9]. Briefly, sedentary behaviors included activities such as reading, general sitting, watching television, or driving. In contrast, light activity included activities such as light cleaning, grocery shopping, yoga, and billiards. Moderate-vigorous activity included activities such as jogging, swimming, and bicycling [9]. Dietary intake was measured using the Arizona Food Frequency Questionnaire (AFFQ). The AFFQ is a validated, semi-quantitative, scannable instrument that evaluates 113-dietary items and asks participants to report usual dietary intake during the prior year [39].

Circulating $1,25(OH)_2D$ and 25(OH)D concentrations were measured at baseline, prior to the start of the intervention. Serum concentrations of vitamin D metabolites were evaluated by Heartland Assays (Ames, IA). Metabolites were measured using established methods, a ^{1,25}I-based radioimmunoassay for $1,25(OH)_2D$ and competitive chemiluminescence immunoassay for 25(OH)D, described previously [40–42]. Blinding and standard quality assurance measures were utilized by the laboratory, and the coefficient of variation is less than 7.0% and 11.5% for 25(OH)D and $1,25(OH)_2D$, respectively [40,42,43].

2.3. Statistical analysis

In a cross-sectional analysis at baseline, vitamin D metabolites were evaluated as continuous variables and by clinical thresholds. Dichotomous variables were created using a clinical threshold for $1,25(OH)_2D$ concentrations (26 pg/ml) [29], whereas proposed thresholds of vitamin D status (20 versus 30 ng/ml) were evaluated for 25(OH)D levels [31,32]. Continuous measures and sex-specific tertiles of light and moderate-vigorous physical activity were compared using adjusted hours per day and METs-hours per day. Sedentary behavior was only evaluated using adjusted hours per day.

Multivariate linear and logistic regression models were employed, and because we found that $1,25(OH)_2D$ and 25(OH)D levels are moderately correlated in this population [44,45], individual models were mutually adjusted for the respective metabolite. Concentrations of $1,25(OH)_2D$ and 25(OH)D were normally distributed in this population [26,44,45] and sensitivity analysis determined that use of the commonly applied log transformation did not significantly change the results (data not shown). We evaluated confounding factors for vitamin D metabolites in this population, as previously described [25,26]. Overall, we assessed including age, body mass index (BMI), sex, race, sleep, current smoking, total energy intake, treatment arm, supplement use, aspirin, seasonality of vitamin D metabolite measurements, as well as dietary intake of various nutrients (Table 1). Confounding variables were included in the final model if the point-estimate changed by 10% or greater, or there was a biological basis for adjustment. Interactions by sex, BMI, and between activity types were also evaluated, using likelihood ratio tests ($\alpha = 0.10$). The STATA statistical software package (version 13.0, Stata Corporation, College Station, TX) was used for all data analysis.

3. Results

Among 876 total participants, the mean age was 66.1 years, and the majority of participants were White (94.3%) and men (66.2%) (Table 1). Individuals with $1,25(OH)_2D$ below the reference value of 26 pg/ml were marginally older with higher BMI, but lower frequency of current cigarette use and higher reported use of aspirin and dietary supplements. In comparison, individuals with insufficient 25(OH)D status (<20 ng/ml) were younger with higher BMI, less frequently White, and more likely to be women and current smokers compared to those with sufficient 25(OH)D. In addition, the insufficient 25(OH)D group used aspirin and supplements less frequently, but also reported higher total energy, calcium, and vitamin D intake.

3.1. Physical activity, sedentary behavior, and vitamin D metabolite levels

Table 2 presents the results of linear regression analyses of vitamin D metabolites and activity. Circulating $1,25(OH)_2D$ concentration was 0.80 pg/ml (95% CI 0.23-1.37) higher per hour increase in moderate-vigorous physical activity per week ($p \leq 0.006$), with all models adjusted for 25(OH)D levels. However, among women, circulating $1,25(OH)_2D$ concentration was 2.31 pg/ml (95% CI 1.06-3.57) higher for every hour increase in moderate-vigorous physical activity per day ($p = 0.001$). In contrast, there was no association among men ($\beta = 0.22$ 95% CI -0.40-0.84; $p = 0.48$; p-interaction = 0.003). Similar associations were observed using MET-hours per day for moderate-vigorous physical activity (p-interaction = 0.004).

Furthermore, for every hour increase in moderate-vigorous activity, 25(OH)D concentration was 1.54 ng/ml higher (95% CI 1.09-1.98; $p = 0.001$) (Table 2). This relationship was similar by sex and no statistically significant interaction was identified ($p = 0.34$). No statistically significant associations were identified between sedentary behavior and circulating $1,25(OH)_2D$ or 25(OH)D levels, with no significant differences by sex (p-interaction = 0.23 and 0.25, respectively). There were also