Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged ≥60 y[1–3]

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ABSTRACT

Background: Vitamin D may improve muscle strength through a highly specific nuclear receptor in muscle tissue.

Objectives: We investigated whether there is an association between 25-hydroxyvitamin D [25(OH)D] concentrations and lower-extremity function in ambulatory older persons, whether that association differs by activity level, and, if so, whether there is an identifiable threshold in the association.

Design: The study was a population-based survey of the ambulatory US population aged 60 to ≥90 y (n = 4100). Lower-extremity function according to serum 25(OH)D concentrations was assessed by linear regression analyses and regression plots after control for activity level (inactive or active) and several other potential confounders. Separate analyses were performed for the timed 8-foot (ie, 2.4 m) walk test and a repeated sit-to-stand test.

Results: The 8-foot walk test compared subjects in the lowest and highest quintiles of 25(OH)D; the latter group had an average decrease of 0.27 s [95% CI: −0.44, −0.09 s (or 5.6%); P for trend < 0.001]. The sit-to-stand test compared subjects in the lowest and highest quintiles of 25(OH)D; the latter group had an average decrease of 0.67 s [95% CI: −1.11, −0.23 s (or 3.9%); P for trend = 0.017]. In the 25(OH)D reference range of 22.5–94 nmol/L, most of the improvement occurred in subjects with 25(OH)D concentrations between 22.5 and ≈40 nmol/L, and further improvement was seen in the range of 40–94 nmol/L. Stratification by activity level showed no significant effect modification.

Conclusion: In both active and inactive ambulatory persons aged ≥60 y, 25(OH)D concentrations between 40 and 94 nmol/L are associated with better musculoskeletal function in the lower extremities than are concentrations < 40 nmol/L. *Am J Clin Nutr* 2004;80:752–8.

KEY WORDS 25-hydroxyvitamin D, lower-extremity function, elderly, community-dwelling adults

INTRODUCTION

Supplementation with vitamin D and calcium has been found to be successful in reducing fracture risk in the elderly. Randomized controlled trials (RCTs) found that nonvertebral fractures decreased by 58% in ambulatory elderly in the United States (1) and by 32% in institutionalized elderly in France (2). A recent 5-y RCT documented a 33% reduction in first hip, wrist, or vertebral fracture in ambulatory elderly living in the United Kingdom who received supplementation with vitamin D only (3). Consistently, in a large cohort study of US nurses, women consuming ≥500 IU vitamin D/d from food plus supplements had a 37% lower risk of hip fracture (relative risk = 0.63; 95% CI: 0.42%, 0.94%) than did women consuming <500 IU vitamin D/d (4).

The protective effect of vitamin D on fractures has been attributed to the established moderate benefit of vitamin D for calcium homeostasis and bone mineral density (1, 5–8). However, an alternative explanation might be that vitamin D affects factors directly related to muscle strength and function (9–14), thus reducing fracture risk through fall prevention, in addition to its benefits on calcium homeostasis. Specifically, in one RCT that compared vitamin D (800 IU/d) plus calcium (1200 mg/d) intakes in institutionalized elderly women with intakes of calcium alone (1200 mg/d), musculoskeletal function improved by 4–11% in the vitamin D plus calcium group (P = 0.0094). In addition, the rate of falling was 49% lower in the vitamin D plus calcium group than in the calcium only group (95% CI: 14%, 71%; P < 0.01; 11).

This effect may be mediated by de novo protein synthesis (10,12), which affects muscle cell growth through a highly specific nuclear receptor expressed in muscle tissue (15, 16). In one study, treatment with 1-α-hydroxyvitamin D increased the relative number and size of Type II muscle fibers in elderly women within 3 mo of treatment (12).

In this study, we investigated whether there is an association between 25(OH)D concentrations and lower-extremity function

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[2] Supported by the Harvard Hartford Foundation, the Kirkland Scholar Award, the Irene and Fredrick Stare Nutrition Education Fund, the Swiss Foundation for Nutrition Research, and the International Foundation for the Promotion of Nutrition Research and Nutrition Education.

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Received January 15, 2004.

Accepted for publication March 8, 2004.

in ambulatory older adults living in the United States, whether any such association differs by activity level, and whether there is an identifiable threshold in this association.

SUBJECTS AND METHODS

Data source and subjects

The third National Health and Nutrition Examination Survey (NHANES III) was conducted between 1988 and 1994 to study the health and nutritional status of a nationally representative sample of the noninstitutionalized US population. The survey oversampled older persons, non-Hispanic black persons, and Mexican Americans.

Interviews were conducted at respondents' homes. Standardized clinical examinations, including blood sampling and functional measurements (8-foot-walk test and sit-to-stand test), in respondents aged ≥60 y were conducted in mobile examination centers and at the homes of participants (17). Of 8375 respondents in that age group, 6866 (82%) consented to an interview and 5740 (69%) were examined in the mobile examination centers. Physical performance tests were performed in 5403 subjects (65%). For this analysis, the final sample consisted of 4100 subjects (49%) aged ≥60 y for whom there were complete data on the timed 8-foot walk test, the repeated timed sit-to-stand test, and serum 25(OH)D concentration. Of these 4100 subjects, 49% were female, 58% were non-Hispanic white, 19% were non-Hispanic black, and 20% were Mexican American. The study protocol for this analysis was approved by the Human Research Committee of the Brigham and Women's Hospital in Boston (Protocol #2003-P-000637/1).

Measurement of lower-extremity function

Lower-extremity function was assessed by using an 8-foot (2.4 m) walking-speed test (8-foot walk test; mean of 2 trials) and a timed test of 5 repetitions of rising from a chair and sitting down (sit-to-stand test). Both tests were previously described in detail (18), were designed to assess lower-extremity function, and were found to accurately predict disability across white (18) and diverse (19) populations. Interrater reliability of 0.93 and test-retest correlations of 0.89 were reported for the 8-foot walk test (18). The previously published test-retest correlation for the sit-to-stand test was 0.73 (20). Verbal instructions and encouragement during the test were standardized (21, 22). Walking aids were allowed for the 8-foot walk test but not for the sit-to-stand test.

Serum concentration of 25(OH)D

Venous blood samples were taken in a standardized fashion in the mobile examination centers. Serum 25(OH)D concentrations were assayed with radioimmunoassay kits (DiaSorin, Stillwater MN; 23). The reference range for the assay is 22.5–94 nmol/L (9–37.6 ng/L).

NHANES III contains an inherent season and latitude structure to the extent that data were collected in the northern latitudes during the summer and in the southern latitudes during the winter. This structure was taken into consideration in analysis of 25(OH)D concentrations because they have been shown to be affected by seasonality and latitude (24).

Data on other covariates

Information on the number of medical comorbidities, self-reported arthritis, activity level, and use of a walking device was obtained in the household interview. For medical comorbidities, a summed score was assessed from 9 comorbid medical conditions: congestive heart disease, stroke, asthma, chronic obstructive pulmonary disease, emphysema, diabetes, hypertension, myocardial infarction, and any cancer.

Respondents were classified as "active" if they walked 1 mile without stopping, swam, jogged, rode a bicycle, danced, exercised, or did garden work in the previous month and "inactive" if they did not perform any of these activities (25). Among active subjects, physical activity intensity was assessed by the metabolic equivalents (METs) on the basis of the physical activities mentioned above. Because inactive subjects did not perform any of these activities, they received 0 METs in this category.

Calcium intake (in mg/d) was calculated from a 24-h dietary recall. The poverty-income ratio (PIR) was computed as the ratio of family income to the poverty threshold as established annually by the Census Bureau after adjustment for changes caused by inflation. Body mass index (BMI, in kg/m^2) was measured in the mobile examination centers.

Statistical analysis

Linear regression models were used to model the association between serum 25(OH)D concentrations and lower-extremity function. Separate analyses were performed for the timed 8-foot walk and the sit-to-stand tests. Serum 25(OH)D concentrations were divided into quintiles. For descriptive statistics, means or proportions were calculated for the different quintiles of 25(OH)D. Crude comparisons shown in **Table 1** used *t* tests and trend tests, and comparisons between races or ethnicities used analysis of variance followed by Bonferroni's correction. The percentage differences in lower-extremity function from lowest to highest quintile of 25(OH)D are based on least-squared means from the linear regression model.

Five covariates—sex, age (5-y categories and <80 y versus ≥80 y), race or ethnicity, calcium intake (<500 or ≥500 mg/d), and activity level (active or inactive)—were considered as potential effect modifiers in separate analyses. For both tests, none of the 5 covariates significantly modified the association between 25(OH)D and lower-extremity function. Therefore, the main results are presented without stratification.

The following potential confounders were included in the linear regression models: sex, age (5-y categories), race or ethnicity, BMI, PIR, daily calcium intake, number of medical comorbidities (0, 1, 2, 3, and ≥4), use of a walking device, self-reported arthritis, and activity level plus METs in active subjects. In addition, the model controlled for the month of assessment to adjust for seasonal changes in vitamin D concentrations (24). The primary results reported account for the NHANES III stratification and clustering but not for the sampling weights (26). This approach was selected because the sampling weights are primarily derived from design variables such as age, sex, race or ethnicity, and PIR. These variables were included in the statistical model, and thus not using the sampling weights offers a good compromise between efficiency and bias. The point estimates are therefore population-based, but they may not be generalizable to the entire noninstitutionalized civilian US population aged >60 y at the time of NHANES III.

TABLE 1
Characteristics of the study population[1]

Variable	Subjects	Overall value	25 (OH)D[2]	8-foot walk test[3,4]	Sit-to-stand test[3,5]
	n (%)		*nmol/L*	*s*	*s*
Age (y)		71.4 ± 7.9[6]	65.7 ± 26.2	3.7 ± 1.6	14.0 ± 4.6
60–64	993 (24)		63.6 ± 25.6	3.4 ± 1.0	13.5 ± 3.9
65–69	880 (22)		65.7 ± 28.8	3.5 ± 1.4	13.5 ± 4.4
70–74	841 (21)		68.2 ± 26.3	3.6 ± 1.3	13.7 ± 4.0
75–79	537 (13)		66.3 ± 25.5	3.9 ± 2.2	14.2 ± 4.6
80–84	588 (14)		65.4 ± 23.5	4.2 ± 1.7	15.0 ± 4.8
85–89	210 (5)		65.0 ± 23.5	4.9 ± 2.2	16.5 ± 8.0
>90	51 (1)		67.4 ± 32.2	5.3 ± 1.8	15.8 ± 5.5
Sex					
Male	2003 (49)		70.2 ± 25.5	3.5 ± 1.2	13.4 ± 4.0
Female	2097 (51)		61.4 ± 26.1	3.9 ± 1.9	14.6 ± 5.1
Activity level					
Active	3055 (75)		68.4 ± 26.2	3.5 ± 1.3	13.4 ± 4.2
Inactive	1045 (25)		57.9 ± 24.6	4.4 ± 2.2	15.8 ± 5.4
Race or ethnicity					
Non-Hispanic white	2399 (58)		71.2 ± 25.4	3.6 ± 1.4	13.7 ± 4.3
Non-Hispanic black	765 (19)		53.8 ± 25.4	3.9 ± 1.6	15.0 ± 5.0
Mexican American	815 (20)		60.0 ± 24.0	4.0 ± 1.9	14.1 ± 4.8
Other	121 (3)		64.9 ± 25.8	4.1 ± 2.0	14.7 ± 5.3
BMI (kg/m^2)		27.1 ± 5.0			
PIR	3649 (89)	2.2 ± 1.9			
25 (OH)D quintiles (nmol/L)					
1	821 (20)		33.8 ± 8.7	4.1 ± 2.2	15.1 ± 5.3
2	827 (20)		50.1 ± 3.8	3.8 ± 1.4	13.9 ± 4.3
3	815 (20)		62.9 ± 3.7	3.7 ± 1.4	14.1 ± 5.1
4	817 (20)		77.2 ± 4.7	3.6 ± 1.6	13.6 ± 4.3
5	820 (20)		104.8 ± 19.7	3.5 ± 1.1	13.4 ± 3.8
Calcium intake (mg/d)		700 ± 469			
Walking device					
Yes	110 (3.6)		60.4 ± 26.9	6.9 ± 4.3	19.5 ± 7.7
No	3990 (97.3)		65.9 ± 26.1	3.6 ± 1.4	13.9 ± 4.4
Number of comorbidities					
0	952 (23)		67.4 ± 25.9	3.5 ± 1.3	13.2 ± 3.8
1	1305 (32)		65.4 ± 25.0	3.6 ± 1.5	13.8 ± 4.5
2	1000 (24)		65.4 ± 27.9	3.8 ± 1.6	14.1 ± 4.7
3	489 (12)		63.5 ± 26.3	4.0 ± 1.6	14.9 ± 5.1
≥4	354 (9)		66.4 ± 25.8	4.2 ± 2.4	15.7 ± 6.0
Self-reported arthritis					
Yes	1812 (44)		64.5 ± 25.4	3.9 ± 1.8	14.7 ± 5.0
No	2288 (56)		66.7 ± 26.7	3.6 ± 1.4	13.5 ± 4.2

[1] $n = 4100$. 25(OH)D, 25-hydroxyvitamin D; PIR, poverty-income ratio.
[2] Significant differences were found between men and women ($P < 0.0001$), active and inactive subjects ($P < 0.0001$), the 3 main race or ethnic groups ($P < 0.0001$), and subjects with and without walking devices ($P = 0.031$).
[3] Significant associations were found with age (P for trend < 0.0001), number of comorbidities (P for trend < 0.0001), and quintiles of 25(OH)D (P for trend < 0.0001); significant differences by sex, activity level, walking device use and nonuse, and self-reported arthritis (all: $P < 0.0001$).
[4] Whites were significantly quicker than were blacks ($P < 0.0001$) and Mexican Americans ($P < 0.0001$).
[5] Both whites ($P < 0.0001$) and Mexican Americans ($P < 0.001$) were significantly quicker than were blacks.
[6] $\bar{x} \pm$ SD (all such values).

To evaluate the dose-response relation more closely and to assess possible thresholds, we conducted a locally weighted regression plot (Lowess) of both the timed 8-foot walk test and the repeated sit-to-stand test on serum 25(OH)D concentrations after adjustment for the same covariates as the linear regression models. The Lowess regression plot is robust and resistant to the influence of outliers, and linearity of the association is not assumed. Statistical analyses were performed with the use of STATA software (version 7.0; Stata Corp, College Station, TX).

RESULTS

Characteristics

Characteristics of the total study population ($n = 4100$) and crude descriptives for 25(OH)D and lower-extremity function (both 8-foot walk and repeated sit-to-stand tests) within subgroups of the population are shown in Table 1. Mean (± SD) age of the total population was 71.4 ± 7.9 y, 49% of the population

TABLE 2
Change in lower-extremity function according to quintiles of 25-hydroxyvitamin D [25(OH)D] concentrations[1]

Model and quintile	25(OH)D range	Crude[2]	Demographics-adjusted[3]	Comorbidity- and activity-adjusted[4,5]
	nmol/L	*s*	*s*	*s*
8-foot (2.4 m) walk test				
1	8.7–43.4	0 (Reference)	0 (Reference)	0 (Reference)
2	43.7–56.7	−0.33[6] (−0.48, −0.19)	−0.25[7] (−0.39, −0.11)	−0.17 (−0.36, −0.02)
3	56.9–69.4	−0.44[6] (−0.59, −0.28)	−0.31[6] (−0.46, −0.17)	−0.22[8] (−0.39, −0.05)
4	69.6–85.9	−0.53[6] (−0.69, −0.38)	−0.31[6] (−0.46, −0.17)	−0.20[8] (−0.36, −0.05)
5	86.1–400.1	−0.67[6] (−0.83, −0.52)	−0.36[6] (−0.51, −0.21)	−0.27[7] (−0.44, −0.09)
Sit-to-stand test				
1	8.7–43.4	0 (Reference)	0 (Reference)	0 (Reference)
2	43.7–56.7	−1.15[6] (−1.60, −0.71)	−0.90[6] (−1.33, −0.47)	−0.68[7] (−1.11, −0.24)
3	56.9–69.4	−0.99[6] (−1.43, −0.55)	−0.61[7] (−1.04, −0.17)	−0.37 (−0.91, 0.16)
4	69.6–85.9	−1.48[6] (−1.92, −1.03)	−0.89[6] (−1.34, −0.45)	−0.57[8] (−1.01, −0.13)
5	86.1–400.1	−1.74[6] (−2.18, −1.30)	−0.96[6] (−1.41, −0.51)	−0.67[7] (−1.11, −0.23)

[1] All values are $\bar{x}$; 95% CI in parentheses.
[2] P for trend < 0.0001 for both tests.
[3] Adjusted for sex, age, BMI, race or ethnicity, and poverty-income ratio. P for trend ≤ 0.0001 for both tests.
[4] Adjusted for sex, age, BMI, race or ethnicity, poverty-income ratio, calcium intake, number of medical comorbidities, self-reported arthritis, use of a walking device, month of assessment, activity level (inactive or active), and outdoor metabolic equivalents in active elderly. P for trend $= 0.001$ (8-foot walk test) and $= 0.017$ (sit-to-stand test).
[5] Accounts for third National Health and Nutrition Examination Survey sampling stratification and clustering.
[6–8] Significantly different from reference value: [6]$P < 0.001$, [7] $P < 0.01$, [8] $P < 0.05$.

was female, and 25% of the population was classified as inactive. Mean 25(OH)D concentrations were lower in inactive subjects (57.9 ± 24.6 nmol/L) than in active subjects (68.4 ± 26.2 nmol/L; $P < 0.0001$) and lower in women (61.4 ± 26.1 nmol/L) than in men (70.2 ± 25.5 nmol/L; $P < 0.0001$).

The subject population was 58% non-Hispanic white, 19% non-Hispanic black, and 20% Mexican American. Mean unadjusted 25(OH)D concentrations were highest in whites (71.5 ± 25.4 nmol/L), intermediate in Mexican Americans (60.0 ± 25.4 nmol/L), and lowest in blacks (53.8 ± 24.0 nmol/L; between-race or between-ethnicity comparisons were significant, $P < 0.0001$). Lower-extremity function test performances decreased with increasing age and with higher numbers of comorbid conditions.

Association between 25(OH)D status and lower-extremity function

The crude and adjusted mean differences for both the 8-foot walk test and the sit-to-stand test by quintiles of 25(OH)D concentrations are shown in **Table 2**. We observed a significant positive association (trend test) between the 8-foot walk test and 25(OH)D concentrations in the crude analysis ($P < 0.0001$) and after control for demographic variables including sex, age, BMI, race or ethnicity, and PIR ($P < 0.0001$). This significant trend was maintained after additional adjustment for number of medical comorbidities, self-reported arthritis, use of a walking device, month of assessment, and activity level (inactive or active and outdoor METs in active elderly) and after sampling stratification and clustering were accounted for ($P = 0.001$). Compared with the lowest quintile of 25(OH)D, the highest quintile showed an average improvement of 0.27 s (5.6%). In addition to the significant trend tests in the 3 different analyses, each quintile of 25(OH)D was significantly different from the reference category.

Similarly, we observed a significant positive association (trend test) between the sit-to-stand test and 25(OH)D concentrations in the crude analysis ($P < 0.0001$) and after control for demographic variables ($P < 0.0001$). The significant positive trend was maintained after additional adjustment for number of medical comorbidities, self-reported arthritis, use of a walking device, month of assessment, activity level (inactive or active and outdoor METs in active elderly) and after sampling stratification and clustering were accounted for ($P = 0.017$). Compared with the lowest quintile of 25(OH)D, the highest quintile showed an average decrease of 0.67s (3.9%). In addition to the significant trend tests in the 3 different analyses, most quintiles of 25(OH)D were significantly different from the reference category.

In the adjusted analyses, active subjects were 0.48 s quicker in the 8-foot walk test and 1.32 s quicker in the sit-to-stand test (both: $P < 0.0001$) than were inactive subjects. However, effect modification by activity level was not present, which suggests that the same improvement in performance speed with increasing 25(OH)D concentrations was found in both active and inactive subjects (vitamin D quintile × activity level interaction: 8-foot walk test, $P = 0.13$; repeated sit-to-stand test, $P = 0.29$).

Regression plots for 25(OH)D status and lower-extremity function

The association between 25(OH)D concentration and lower-extremity function is illustrated in the regression plots of **Figure 1** A and B. In both tests performance speed continued to increase throughout the reference range of 25(OH)D (22.5–94 nmol/L), and most of the improvement occurred at 25(OH)D concentrations from 22.5 to ≈40 nmol/L. Further improvement was seen

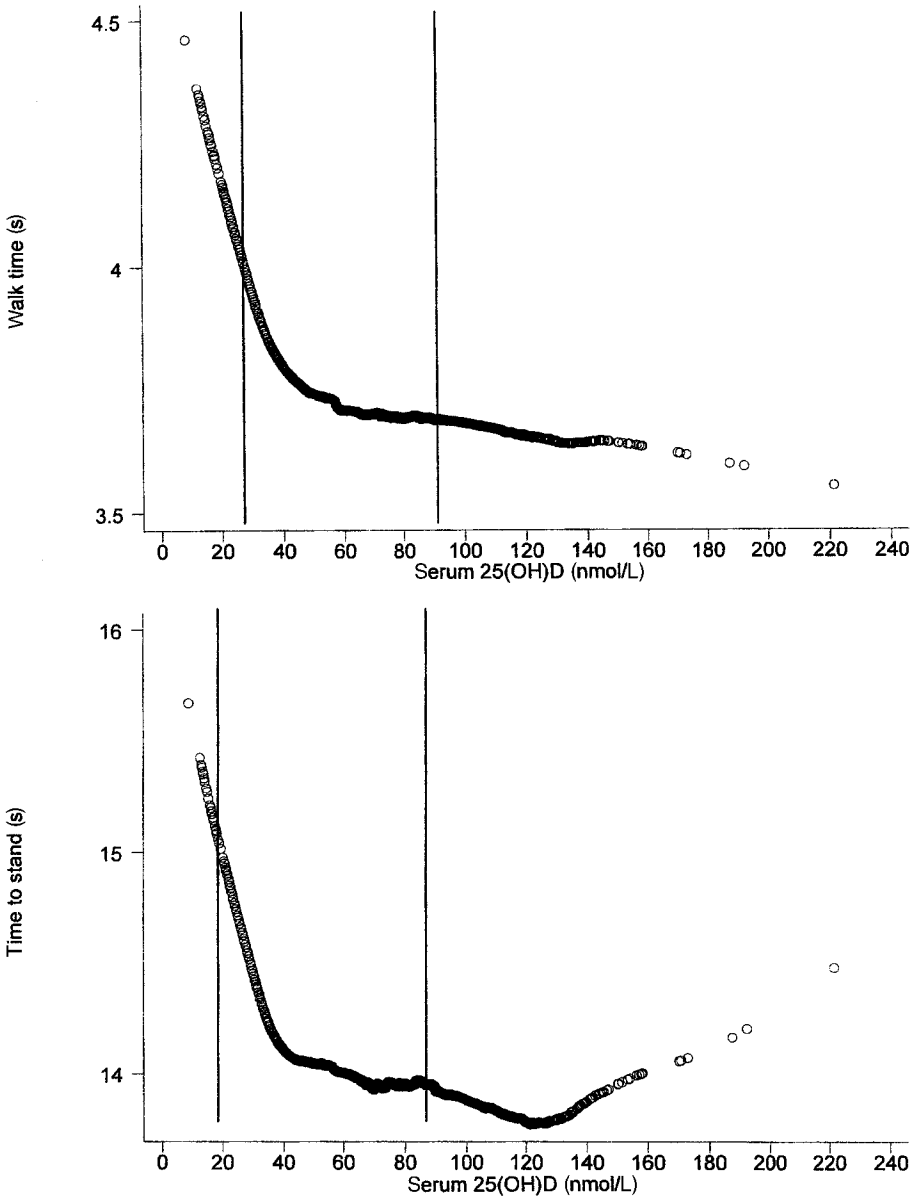

FIGURE 1. Lowess regression plots of lower-extremity function on the 8-foot (ie, 2.4 m) walk test and the sit-to-stand test by 25-hydroxyvitamin D [25(OH)D] concentrations. Plots are adjusted for sex, age, race or ethnicity, BMI, calcium intake, poverty-income ratio, number of medical comorbidities, self-reported arthritis, use of a walking device, month of assessment, activity level (inactive or active), and metabolic equivalents in active elderly. The reference range for the 25(OH)D assay of 22.5–94 nmol/L (9–37.6 ng/L) is marked as vertical lines in both panels.

in the range of 40–94 nmol/L, but the magnitude was much less dramatic. Only for the sit-to-stand test did there appear to be a decline in performance speed at the highest 25(OH)D concentrations (>120 nmol/L), but this finding is based on a relatively small number of observations (3.3% of population).

Other factors predicting lower-extremity function in the adjusted analyses

For the 8-foot walk test, after control for quintiles of 25(OH)D, other significant predictors of function were, in order of importance, the use of a walking device (an increase of 2.6 s), age [increases of 0.07, 0.27, 0.58, 0.88, 1.41, and 1.45 s for categories of 65–69, 70–74, 75–79, 80–84, 85–89, and >89 y, respectively (category of 60–64 y is reference category)], Mexican American ethnicity (increase of 0.58 s; reference category is white race), black race (increase of 0.39 s; reference category is white race), being inactive (increase of 0.48 s), female sex (increase of 0.22 s), higher PIR (increase of 0.10 s), self-reported arthritis (increase of 0.10 s), presence of comorbid condition (increase of 0.08 s), and higher BMI (increase of 0.02 s).

For the repeated sit-to-stand test, after control for quintiles of 25(OH)D, other significant predictors of function were, in order of importance, the use of a walking device (increase of 4.1 s), age [increase of 0.39, 0.55, 1.39, and 2.70 s for categories of 70–74, 75–79, 80–84, and 85–89 y, respectively (category of 60–64 y is reference category)], being inactive (increase of 1.32 s), black race (increase of 1.11 s; reference category is white race), being female (increase of 0.67 s), self-reported arthritis (increase of 0.56 s), presence of comorbid condition (increase of 0.32 s), and higher PIR (increase of 0.31 s).

DISCUSSION

The 2 main targets for prevention of osteoporotic fractures in older persons are reduction in bone loss and reduction in the risk of falls. Thus treatments that may act through both of these targets are of high clinical value, especially if a possible intervention offers high compliance through a well-tolerated, inexpensive, and safe supplement, such as vitamin D.

In this population-based sample of US ambulatory adults aged ≥60 y, we found a significant positive association between 25(OH)D concentrations and lower-extremity function. This was consistent for both performance tests and was present after adjustment for age, sex, race or ethnicity, PIR, use of a walking aid, BMI, number of comorbid conditions, self-reported arthritis, month of assessment, and activity level. Lower-extremity function improved continuously with higher 25(OH)D concentrations throughout the reference range. However, most of the improvement occurred in 25(OH)D concentrations between the lowest values and ≈40 nmol/L. Further improvement was seen in the range of 40–94 nmol/L, but the change was much less dramatic. Lower- extremity function improved between 3.9% (sit-to-stand test) and 5.6% (8-foot walk test) from the lowest to the highest quintile of 25(OH)D concentrations.

Guralnik et al showed that both tests accurately predict disability across white (18) and diverse (19) populations. In other prospective studies, walking speed was a significant fall-related predictor of hip fracture [EPIDOS Study (27): relative risk = 1.4 for 1 SD decrease; 95% CI: 1.1, 1.6], whereas the inability to rise from a chair doubled the risk for a hip fracture [SOF Study (28): relative risk = 2.1; 95% CI: 1.3, 3.2]. Thus an association between these tests and 25(OH)D concentrations is clinically relevant.

A possible explanation for the association between vitamin D and lower-extremity function is that 1,25-hydroxyvitamin D, the active vitamin D metabolite, binds to a highly specific nuclear receptor in muscle tissue (16, 29), which leads to de novo protein synthesis and thus to muscle cell growth (10, 12). Glerup et al (30) suggested that vitamin D–deficient subjects show severely impaired muscle function before biochemical signs of bone disease appear.

There is some support in the literature for our observation that higher 25(OH)D concentrations in the elderly may be preferable to lower concentrations with regard to musculoskeletal function. Low 25(OH)D concentrations have been documented in institutionalized elderly in Australia who were prone to falling (31), and leg extension power was significantly decreased in ambulatory elderly Swiss men and women with low 1,25-dihydroxyvitamin D concentrations (32). In recently hospitalized older patients and randomly selected ambulatory elderly in Norway, higher 25(OH)D concentrations were correlated with better muscle strength, improved musculoskeletal function, and fewer falls (33).

The positive associations between vitamin D and musculoskeletal function observed in these cross-sectional studies are supported by 2 RCTs. In ambulatory elderly women in Germany, a study comparing a 2-mo treatment with vitamin D (800 IU/d) plus calcium (1200 mg/d) with treatment with calcium alone (1200 mg/d) found that body sway decreased significantly, by 9%. In the vitamin D–treated group, mean 25(OH)D concentrations increased from 25.7 ± 13.6 to 40.5 ± 27.0 nmol/L (34). In institutionalized elderly women in Switzerland, supplementation with vitamin D (800 IU/d) plus calcium (1200 mg/d) significantly reduced the risk of falling by 49% (95% CI: 14%, 71%) within 3 mo, bringing mean 25(OH)D concentrations from 41.0 ± 25.5 to 65.0 ± 23.8 nmol/L (11). In addition, a significant improvement in grip strength, knee extensor and flexor strength, and the timed "up and go" test (35) was observed in the group treated with vitamin D plus calcium (summed musculoskeletal score: $P = 0.0094$; 4–11% improvement over time, depending on test).

Added to the above published reports, our results suggest that a positive association between 25(OH)D and musculoskeletal function does exist in ambulatory subjects aged ≥60 y in the United States, independent of activity level, sex, age, race or ethnicity, and calcium intake.

This study confirms the high prevalence of low 25(OH)D concentrations in the general older population and an even higher prevalence in blacks (36, 37). The vitamin D intakes needed to increase 25(OH)D to desirable concentrations of 90–100 nmol/L exceed the currently recommended intakes of 400 IU/d for those aged 51–70 y and 600 IU/d for those aged >70 y (38), but even low-dose supplementation may increase the 25(OH)D concentrations in most of the older population to >40 nmol/L. Supplementation of vitamin D with 700–1000 IU/d bring mean 25(OH)D concentrations to 90–100 nmol/L (1, 39–41). The intake needed to bring most adults to this 25(OH)D range has not, however, been defined.

For the sit-to-stand test, there may be a trend toward impaired function at the highest 25(OH)D concentrations, those >120 nmol/L. This could be due to the fact that those in the highest 25(OH)D quintiles have been treated with vitamin D because of osteoporosis and muscle weakness. Another potential explanation is that higher 25(OH)D concentrations are toxic to lower-extremity function in the elderly. However, the number of observations in persons with 25(OH)D concentrations >120 nmol/L was small, and we did not observe a decline in function in the 8-foot walk test at the highest concentrations of 25(OH)D.

Among the main strengths of the study is its population-based design. In addition, the consistency of the association between 25(OH)D and lower-extremity function across both tests lends credibility to the main findings. Finally, the endpoint, lower extremity function, is important through its strong predictive value in regard to disability, falls, and hip fractures in older adults (18, 19, 27, 28).

The study also has limitations, one of which is the cross-sectional design of the analyses, which cannot be used to establish a causal relation between vitamin D concentrations and lower-extremity function. However, a causal relation between vitamin D and musculoskeletal function was shown in 2 RCTs (11, 34), and biologic mechanisms that explain the relation between vitamin D and musculoskeletal function seem plausible in the light of the literature discussed (10, 12, 15, 16). The original survey has a potential for response bias, which we attempted to accommodate by using the NHANES III adjustments for sampling stratification and clustering.

In conclusion, in both active and inactive ambulatory US men and women aged ≥60 y, higher concentrations of 25(OH)D are associated with better musculoskeletal function in the lower extremities. For optimal lower-extremity function, it is desirable to reach 25(OH)D concentrations of ≥40 nmol/L, and concentrations as high as the upper end of the reference range (90–100 nmol/L) appear to be advantageous. Given the high prevalence of low 25(OH)D concentrations and inactivity in this national survey and the positive association between 25(OH)D and lower-extremity function, vitamin D supplemention may offer a way to

improve lower-extremity function in both active and inactive subjects aged ≥60 y.

The analysis was planned by HAB-F, TD, JEO, and BD-H. HAB-F conducted the analysis with contributions by TD, JEO, BDH, and FBH. All authors evaluated the results and contributed to their interpretation. HAB-F wrote the manuscript with input from all authors.

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