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25(OH) Vitamin D is Associated with Greater Muscle Strength in Healthy Men and Women

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Abstract

Purpose—The purpose of the study was to examine the relationship between serum 25-hydroxy vitamin D (25(OH)D) levels and muscle strength in 419 healthy men and women over a broad age range (20-76 years of age).

Methods—Isometric and isokinetic strength of the arms and legs was measured using computerized dynamometry and its relation to vitamin D was tested in multivariate models controlling for age, gender, resting heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), maximal oxygen uptake (VO_{2max},), physical activity counts, and season of vitamin D measurement.

Results—Vitamin D was significantly associated with arm and leg muscle strength when controlling for age and gender. When controlling for other covariates listed above, vitamin D remained directly related to both isometric and isokinetic arm strength but only to isometric leg strength.

Conclusion—These data suggests that there may be a differential effect of vitamin D on upper and lower body strength. The mechanism for this difference remains unclear but could be related to differences in androgenic effects or to differences in vitamin D receptor expression. Our study supports a direct relationship between vitamin D and muscle strength and suggests that vitamin D supplementation be evaluated to determine if it is an effective therapy to preserve muscle strength in adults.

Keywords

25-Hydroxyvitamin D; Dynamometry; Androgen; VDR

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Introduction

Paragraph Number 1 Higher serum 25-hydroxy vitamin D (25(OH)D) concentrations are associated with improved cardiovascular outcomes(18), enhanced immune function(6), and a reduced incidence of cancer(15). Higher serum vitamin D concentrations have also been associated with greater muscle strength and performance in some (10, 11, 14, 16, 27, 31, 33), but not all (2, 8, 30)studies. Some studies measured single muscle group performance such as that measured by handgrip (8, 14) or leg strength (10, 11, 16, 27, 31, 33) and have been restricted to young (14, 31) or elderly (11, 16, 33)subject groups. The present study measured 25(OH)D concentrations and tested strength in multiple muscle groups in 419 healthy adults as part of the Effects of *ST*atins *O*n skeleletal *M*uscle function and *P*erformance (STOMP) study (29) (R01HL081893). Muscle strength and vitamin D was compared to address the above discrepancies among previous research studies.

Methods

Study Sample

Paragraph Number 2 Data were obtained from healthy men and women enrolled in the STOMP study, a randomized double-blind clinical trial investigating the effect of atorvastatin 80 mg daily on skeletal muscle strength and exercise performance (29). The STOMP study was approved by the Hartford Hospital Institutional Review Board. Written informed consent was obtained from all participants. The STOMP population consisted of 205 men and 214 women, ≥20 years of age, recruited from study sites at Hartford Hospital, the University of Massachusetts-Amherst, and the University of Connecticut-Storrs. Baseline data for STOMP included anthropometrics, vital signs, serum 25(OH)D concentrations and strength measurements, the later performed over 3 days prior to randomization to either statin or placebo. The first day of strength testing was designed for practice in the testing procedures and was not used in data analysis. Results from the second and third days of strength testing were averaged for each subject to minimize day-to-day variation.

Anthropometrics, Vitals and Baseline Activity Levels

Paragraph Number 3 Weight was determined using a calibrated balance beam scale. Height was measured using a wall-mounted tape measure. Body mass index (BMI) was calculated by dividing the participants' weight in kilograms by height in meters squared. Resting blood pressure was determined with a Welch Allyn floor sphygmomanometer after subjects were seated with their back supported for 5 minutes of rest and the arm positioned at heart level (7). Resting pulse was obtained using an electronic heart rate monitor. Participant's physical activity was recorded over a 96-hour period utilizing an Actiwatch accelerometer (Actigraph, Pensicola, FL). Physical activity was determined to control for variations in activity among subjects. Maximal oxygen uptake (Vo_{2max}) was determined after an 8-12 hour fast using a modified Balke treadmill protocol (1) and breath-by-breath analysis of expired gases using a ParvomedicsTrueOne 2400 metabolic cart (ParvoMedics Corporation, Sandy, Utah).

Serum 25-OH Vitamin D Assay

Paragraph Number 4 Serum 25(OH)D was used to assess vitamin D status (4). Serum 25(OH)D was determined at the first baseline visit using an enzyme-linked immunosorbent assay (Clinical Laboratory Partners, Newington, Connecticut). Serum samples were collected throughout the calendar year and classified as winter (December to February), spring (March to May), summer (June to August), and fall (September to November) samples (3) to account for possible seasonal variation in vitamin D levels (17).

Muscle Strength and Exercise Performance Assessment

Paragraph Number 5 Dominant hand isometric strength was measured using a calibrated Jamar hydraulic handgrip dynamometer (Lafayette Instrument Company, Lafayette, IN). Three maximal contractions lasting 3 seconds each with one minute rest between were recorded. An average of the 3 contractions was used as the criterion score. Dominant elbow flexion/extension and knee flexion/extension strength was measured with isometric and isokinetic testing protocols using a Biodex System 3 dynamometer (Biodex Medical, Shirley, NY). This system is a valid method for determining torque produced by these muscle groups (12). Participants warmed up by performing 3 submaximal contractions before each test. For the elbow isometric testing, subjects completed 3 maximal flexion and extension contractions with the elbow flexed at a 90 degree angle. After 5 minutes rest, participants performed elbow isokinetic testing consisting of 4 maximal contractions in succession at 1.05 rad/s (60 deg/s). Participants rested for another 5 minutes before performing the same maneuver at 3.14 rad/s (180 deg/s). Isometric knee testing was performed with the knee flexed at a 110 degree angle. Subjects performed 3 maximal flexion and extension contractions. After 5 minutes rest, participants performed isokinetic knee testing consisting of 4 maximal continuous contractions at 1.05 rad/s (60 deg/s). They rested for another 5 minutes before performing 4 maximal continuous contractions at 3.14 rad/s (180 deg/s). Average peak torque was calculated using the Biodex System 3 Software for all strength tests. Data between baseline visits 2 and 3 were averaged as the criterion score.

Statistical Methods

Paragraph Number 6 The variable of interest was average peak torque (APT) for each of the Biodex muscle tests and kilograms of force with handgrip. Strength variables and vitamin D were not normally distributed, so data were log-transformed for analyses. For variables that were log transformed before modeling, the mean shown is the back-transformed mean of the log transform, and the dispersion is a coefficient of variation (%). Group differences in baseline characteristics between men and women were compared using one-way analysis of variance ANOVA. Univariate associations between vitamin D and strength were investigated using Pearson product-moment correlation coefficients. Relationships between vitamin D and strength were determined with age and gender controlled for in the ANOVA model. If there was a significant effect of vitamin D on strength with age and gender included, the relative influence of other predictors was investigated using multiple linear regression to determine if vitamin D remained significant and to determine the relative influence of each variable based on the partial correlation coefficient. The variables added to the model were: resting heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), VO_{2max}, physical activity counts, and season of vitamin D measurement. All two-way interactions between predictors were considered in multivariate models. Statistical significance was accepted at $p \leq 0.05$. All analyses were performed using SPSS Statistics 15.0 (IBM Corporation, New York).

Results

Paragraph Number 7 Data from 419 healthy adults were analyzed, of whom 214 (52%) were women (Table 1). In the present study, 1% of subjects had a serum vitamin D level less than 10 ng/dl, 7% had vitamin D levels between 10 and 20 ng/mL, 27% had vitamin D levels between 20 and 30 ng/mL, and 65% had a vitamin D level above 30 ng/mL. Age affected all baseline characteristics ($p < 0.01$ for all) except for resting HR, BMI, and physical activity counts. Season of phlebotomy was also significantly related to vitamin D status (both $p <$ 0.001). There was a statistically significant difference between men and women for all mean strength values expressed as average peak torque in Newton-meters (Nm) (Table 2).

Univariate correlations between serum 25(OH)D and the average peak torque of the strength tests were not significant.

Relation Between Vitamin D and Arm Strength

Paragraph Number 8 With age and gender included in the model, vitamin D was positively associated with 6 of 7 arm strength measurements (Table 3). Handgrip was the only arm strength measurement that did not reach significance ($p = 0.77$). Vitamin D remained a significant predictor of arm strength even with multivariate analysis controlling for all other relevant baseline factors (Table 4).

Relationship Between Vitamin D and Leg Strength

Paragraph Number 9 With age and gender included in the model, vitamin D was positively associated with 4 of 6 leg strength variables (Table 3), but most of these significant relationships between vitamin D and lower body strength disappeared with multivariate analysis. Only 2 out of the 4 remained significant in the multivariate analysis (Table 4).

Discussion

Paragraph Number 10 This is to our knowledge the first large cross sectional study investigating the relationship between vitamin D status and arm and leg muscle strength in a wide age range of healthy adults. We have documented that higher vitamin D levels are associated with both arm and leg muscle strength after adjusting for age and gender. Only the association between arm isometric and isokinetic strength and vitamin D remains consistently positive, however, after controlling for confounders associated with muscle strength including HR, SBP, DBP, BMI, VO_{2max}, physical activity counts, and season of phlebotomy. The association of serum 25(OH)D levels with leg strength was less robust and only knee isometric strength remained significant in multivariate analyses.

Paragraph Number 11 There are few studies examining the relationship between vitamin D status and muscle strength of the arms and hands. Serum 1,25 $(OH)_2$ vitamin D concentrations correlated directly with biceps force ($p = 0.024$) in a cohort of 211 elderly men between the ages of 71 and 86 (28). Serum 25(OH)D levels were also directly related to abduction ($p = 0.001$) and external rotation ($p < 0.001$) torque of shoulder muscles in men and women with rotator cuff disorders (22). Similarly, serum 25(OH)D was directly related to handgrip strength in 435 men ($p = 0.004$) and 541 women ($p = 0.01$) ≥65 years of age (19) as well as among 70 women ($p < 0.05$) over the age of 65 whose 25(OH)D concentrations ranged from 8 to 20 ng/mL (20). The rare study examining individuals across the adult age range has failed to observe a consistent relationship between serum vitamin D and upper body strength, measured as handgrip (8). We observed a direct relationship between 25(OH)D and upper arm strength in both men and women across the adult age range suggesting that this effect of vitamin D is not limited to older subjects.

Paragraph Number 12 There are also few studies examining the relationship between vitamin D status and leg muscle strength as determined by computerized dynamometer. Vitamin D levels less than 30 ng/mL were associated with poor thigh isometric extension ($p = 0.020$) and flexion ($p = 0.032$) performance measured by Biodex testing in women 75 years of age (16). The present study also found a direct relation between 25(OH)D levels with isometric knee strength in both men and women over a broad age range (20 to 76), but this relationship did not persist when leg strength was tested in the isokinetic environment.

Paragraph Number 13 Vitamin D deficiency affects type II skeletal muscle fibers and can produce a myopathy. Type II muscle fiber atrophy of the intercostals muscles has been reported in two cases of patients with osteomalacic myopathy and vitamin D levels less than

30 ng/mL (32). Middle gluteal muscle samples from elderly women with vitamin D deficiency (<15.6 ng/mL) also show type II muscle fiber atrophy compared to individuals with higher vitamin D levels (>15.6 ng/mL). Furthermore, when serum 25(OH)D levels were less than 15.6 ng/mL, the mean type II fiber diameter correlated with vitamin D status ($r = 0.714$, $p = 0.0011$) (24). Similarly, when 1,000 IU of vitamin D were provided daily for 2 years to 96 elderly women with vitamin D deficiency (<10 ng/mL) in a randomized, placebo controlled trial, the type II muscle fibers of the vastus lateralis in the vitamin D group increased an average of 96.5% in diameter whereas the untreated group experienced a 22.5% decrease in diameter ($p < 0.0001$), and the diameter of type II muscle fibers correlated with serum 25(OH)D concentrations ($r = 0.558$, $P < 0.0001$) (25). There was also a 59% reduction in falls with vitamin D supplementation in that study (25). Such results suggest that the effect of vitamin D may vary with the fiber type of the muscle, but also suggest that vitamin D supplementation may have important clinical effects.

Paragraph Number 14 We observed stronger and more consistent associations between vitamin D levels and muscle strength in the arms than in the legs. This observation agrees with the literature cited above, but the explanation for this difference is unclear. Since serum 25(OH)D levels appear to affect type II muscle fibers, differences in fiber type composition between the arms and legs could be responsible. In the rat, the biceps brachii are composed of 95% type II fibers whereas the vastus intermedius is composed of only 36% type II fibers(9). There are few studies on fiber type distribution in humans. One study looked at fiber type distribution from 32 recent post-mortem humans and found that vastus intermedius was composed of 53% of type II fibers whereas the vastus lateralis was composed of 68% type II fibers (13). This study only examined leg muscles and did not investigate differences between upper and lower body muscle groups. Alternatively, since the effects of vitamin D on skeletal muscle are mediated through the vitamin D receptor (VDR)(5), differences in VDR concentrations between different muscle groups could contribute to our observed differential effects between the arms and the legs, but we are unaware of studies examining differences in VDR expression in arm and leg muscles. Another explanation for the differential effect of Vitamin D on upper and lower body strength may be attributable to a greater utilization of lower extremities during daily, load bearing exercise which thus increases modulation of leg strength by stimuli such as environment and lifestyle.

Paragraph Number 15 Another possible reason for the stronger association of 25(OH)D levels with the arms rather than the legs could be androgenic effects. Androgens are known to produce larger effects on the upper body musculature. Oxymetholone, an oral androgen, administered to older men increased upper body strength compared to placebo, but did not significantly increase leg strength (26). Vitamin D supplementation increases serum testosterone levels in men. Middle aged men treated with 3332 IU of vitamin D increased total testosterone, biologically active testosterone and free testosterone when compared to baseline over men treated with placebo (23). How vitamin D increases androgen levels is unclear, but it may decrease the aromatization of testosterone to estrogen. Vitamin D decreases aromatase mRNA expression in breast cancer cells, which would increase testosterone levels and decrease estrogen production, but increases aromatase gene expression in adrenocortical and prostate cancer cells. (21). We did not measure androgen levels in the present study so we cannot determine if the effect on upper body strength was due to an interaction between vitamin D status and androgenic activity.

Paragraph Number 16 There are limitations to this study. We did not determine vitamin D intake via diet or supplementation so we cannot determine if differences in vitamin D levels were due to sun exposure or oral intake. We did not measure other serum factors related to vitamin D metabolism including calcium, parathyroid hormone, phosphorus and sex hormones levels so we cannot determine whether these could have contributed to the "vitamin D effect". Despite these limitations, our results demonstrate that vitamin D levels are directly associated with both arm and leg muscle strength, although the later association only persisted during isometric testing and not isokinetic testing. These results suggest that vitamin D should be studied as a technique to maintain muscle strength and especially arm muscle strength, in aging adults.

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Table 1

Subject Characteristics (n = 419)

Variable	Total	Men (n = 205)	Women (n = 214)	*p* Value*
Serum 25-hydroxy vitamin D (ng/mL)	33.6 (11%)	32.1 (10%)	35.1 (11%)	<0.01
Age	44 ± 16.1	43 ± 15.8	44 ± 16.4	0.67
BMI	26 ± 4.8	27 ± 4.5	25 ± 4.9	<0.01
Resting pulse (bpm)	69 ± 11.1	67 ± 11.8	70 ± 10.4	<0.01
Seated blood pressure systolic (mmHg)	119 ± 13.3	122 ± 12.8	116 ± 13.4	<0.01
Seated blood pressure diastolic (mmHg)	75 ± 9.6	77 ± 9.4	74 ± 9.9	0.02
Maximal oxygen uptake (ml/kg/min)	33.9 ± 9.7	38.2 ± 8.9	30.2 ± 8.8	<0.01
Physical activity (counts per day)	190730±140999	210991±173778	171157±96064	<0.01
Season (Serum 25-hydroxy vitamin D measurement)				0.13
Spring	130 (31%)	54 (26%)	76 (35%)	
Summer	122 (29%)	65 (32%)	57 (27%)	
Fall	92 (22%)	50 (24%)	42 (20%)	
Winter	75 (18%)	36 (18%)	39 (18%)	

Values are presented as mean ± SD or number (percentage)

Since serum 25-hydroxy vitamin D was not normally distributed, values are presented as geometric mean (coefficient of variation %)

*for gender difference

Table 2

Mean Strength Values (n = 419)

Test Type		Total	Men (N=205)	Women (N=214)	*p* Value*
Handgrip					
	Handgrip	37 (9%)	47 (6%)	29 (8%)	<0.01
Elbow					
	Isometric Extension APT	40 (12%)	56 (8%)	29 (8%)	<0.01
	Isometric Flexion APT	48 (11%)	66 (6%)	35 (8%)	<0.01
	Isokinetic Extension 60°/sec APT	37 (11%)	49 (6%)	27 (8%)	<0.01
	Isokinetic Flexion 60°/sec APT	32 (12%)	46 (6%)	22 (7%)	<0.01
	Isokinetic Extension 180°/sec APT	30 (12%)	41 (8%)	22 (9%)	<0.01
	Isokinetic Flexion 180°/sec APT	28 (11%)	39 (6%)	21 (7%)	<0.01
Knee					
	Isometric Extension APT	178 (8%)	227 (6%)	141 (7%)	<0.01
	Isometric Flexion APT	77 (9%)	99 (6%)	60 (8%)	<0.01
	Isokinetic Extension 60°/sec APT	137 (8%)	177 (5%)	107 (6%)	<0.01
	Isokinetic Flexion 60°/sec APT	70 (10%)	93 (6%)	53 (9%)	<0.01
	Isokinetic Extension 180°/sec APT	92 (9%)	121 (6%)	71 (7%)	<0.01
	Isokinetic Flexion 180°/sec APT	49 (11%)	67 (7%)	37 (10%)	<0.01

Strength values are represented by average peak torque (APT) in Newton-meters (Nm) and presented as geometric mean (coefficient of variation %)

*for gender difference

Table 3

ANOVA results between Vitamin D and Strength for between-subject effects when Age and Gender were controlled (F statistics/*p* value)

	Log Serum 25-hydroxy vitamin D	
Test Type	**F**	***p* value**
Handgrip		
Handgrip	0.087	0.77
Elbow		
Isometric Extension APT	4.115	0.04
Isometric Flexion APT	5.540	0.02
Isokinetic Extension 60°/sec APT	5.301	0.02
Isokinetic Flexion 60°/sec APT	6.906	0.01
Isokinetic Extension 180°/sec APT	8.133	0.01
Isokinetic Flexion 180°/sec APT	4.357	0.04
Knee		
Isometric extension APT	4.562	0.03
Isometric flexion APT	7.335	0.01
Isokinetic Extension 60°/sec APT	2.321	0.13
Isokinetic Flexion 60°/sec APT	5.668	0.02
Isokinetic Extension 180°/sec APT	2.468	0.12
Isokinetic Flexion 180°/sec APT	4.833	0.03

ANOVA results assessing the relationship between Vitamin D and Strength variables when age and gender were controlled for in the model.

Table 4

Multivariate Regression (partial correlation coefficients/ *p* values) for strength variables that were significantly associated with Vitamin D from Table 3

Test Type		Partial Correlation Coefficient	*p* Value	R Square
Elbow				
Isometric Elbow Extension APT				0.725
	Vit D	0.114	0.02	
	Gender	−0.661	<0.01	
	Age	−0.224	<0.01	
	BMI	0.322	<0.01	
	VO_2 Max	0.454	<0.01	
Isometric Elbow Flexion APT				0.685
	Vit D	0.098	0.05	
	Gender	−0.669	<0.01	
	Age	−0.256	<0.01	
	BMI	0.203	<0.01	
	VO_2 Max	0.123	0.01	
	DBP	0.155	<0.01	
Isokinetic Elbow Extension 60°/sec APT				0.690
	Vit D	0.113	0.02	
	Gender	−0.630	<0.01	
	Age	−0.145	<0.01	
	BMI	0.350	<0.01	
	VO_2 Max	0.251	<0.01	
Isokinetic Elbow Flexion 60°/sec APT				0.793
	Vit D	0.140	0.01	
	Gender	−0.789	<0.01	
	Age	−0.128	0.01	
	BMI	0.336	<0.01	
	VO_2 Max	0.136	0.01	
Isokinetic Elbow Extension 180°/sec APT				0.635
	Vit D	0.123	0.01	
	Gender	−0.589	<0.01	
	Age	−0.114	0.02	
	BMI	0.336	<0.01	
	VO_2 Max	0.205	<0.01	
Isokinetic Elbow Flexion 180°/sec APT				0.734

Test Type		Partial Correlation Coefficient	*p* Value	R Square
	Vit D	0.116	0.02	
	Gender	−0.735	<0.01	
	Age	−0.118	0.02	
	BMI	0.312	<0.01	
	VO_2 Max	0.110	0.03	
Knee				
Isometric knee extension APT				0.492
	Vit D	0.108	0.03	
	Gender	−0.610	<0.01	
	Age	−0.440	<0.01	
	DBP	0.116	<0.01	
	BMI	0.107	0.03	
Isometric knee flexion APT				0.617
	Vit D	0.138	0.01	
	Gender	−0.702	<0.01	
	Age	−0.567	<0.01	
	DBP	0.122	0.01	
	BMI	0.111	0.03	
Isokinetic Knee Flexion 60°/sec APT				0.644
	Vit D	0.090	0.07	
	Gender	−0.551	<0.01	
	Age	−0.289	<0.01	
	BMI	0.296	<0.01	
	VO_2 Max	0.231	<0.01	
Isokinetic Knee Flexion 180°/sec APT				0.586
	Vit D	0.068	0.17	
	Gender	−0.489	<0.01	
	Age	−0.176	<0.01	
	BMI	0.278	<0.01	
	VO_2 Max	0.264	<0.01	

Multiple linear regression analysis of serum 25-hydroxy vitamin D (Vit D) and the significant strength variables associated with Vitamin D in the ANOVA models. Predictors included in the multivariate analyses were age, gender, pulse, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), maximal oxygen uptake (VO_2 Max), physical activity counts, and season of vitamin D blood draw, as were all two-way interactions. R square values for each regression model are presented.