Relation of Vitamin D Level to Maximal Oxygen Uptake in Adults

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Low cardiorespiratory fitness and low serum 25-hydroxy vitamin D (25[OH]D) levels are associated with increased cardiovascular and all-cause mortality, but whether low 25(OH)D is independently associated with cardiorespiratory fitness in healthy adults is not known. We examined 25(OH)D levels and fitness in 200 healthy adults participating in a double-blind clinical trial investigating statins and muscle performance (STOMP study). Maximal aerobic exercise capacity (Vo_{2max}) was measured using metabolic gas analysis during graded treadmill exercise to exhaustion. 25(OH)D was measured using an enzyme-linked immunosorbent assay. Daily physical activity was assessed using the Paffenbarger Physical Activity Questionnaire. Serum 25(OH)D concentration was positively related to Vo_{2max} ($r = 0.29$, $p = 0.0001$), even after adjusting for relevant predictors (e.g., age, gender, and body mass index). There was also a significant interaction between 25(OH)D level and self-reported hours of moderate to vigorous physical activity (MVPA; $p < 0.02$). With each SD increase in 25(OH)D, Vo_{2max} increased by 2.6 ml/kg/min ($p = 0.0001$) when MVPA was low (16 hours/week) and 1.6 ml/kg/min ($p < 0.0004$) when MVPA was moderate (35 hours/week) but only 0.01 ml/kg/min ($p = 0.9$) when MVPA was high (64 hours/week). In conclusion, serum 25(OH)D levels predict Vo_{2max} in adults; the effect is greatest in those with low levels of physical activity. © 2011 Elsevier Inc. All rights reserved. (Am J Cardiol 2011;xx:xxx)

Vitamin D (25[OH]D) deficiency is present in approximately 50% of adults in the United States[1,2] and is associated with increased cardiovascular (CV) events and overall mortality.[3–5] Vitamin D deficiency may affect CV morbidity and mortality by its effect on CV risk factors such as increased blood pressure and incidence of type 2 diabetes.[6–8] Poor cardiorespiratory fitness is an additional independent risk factor for CV morbidity and mortality,[9,10] and cardiorespiratory fitness, measured as maximal oxygen consumption (Vo_{2max}), has recently been shown to be directly related to serum vitamin D in 59 healthy young women.[11] The present study examined the relation of 25-hydroxy vitamin D (25[OH]D) levels to cardiorespiratory fitness in a larger cohort of men and women.

Methods

Baseline data were collected on 200 adults free of overt CV and metabolic disease who were participating in a double-blind clinical trial investigating the effect of STatin Medications On skeletal Muscle Performance (STOMP study).[12] Subjects were not taking medications known to affect serum lipids, blood pressure, or muscle metabolism. Before statin or placebo treatment, subjects completed 3 study visits over a period of 2 weeks. Participants underwent a modified Balke treadmill test to determine Vo_{2max}.[13] Vo_{2max} and ventilatory threshold were determined using breath-by-breath analysis of expired gases with a Parvomedics TrueOne 2400 metabolic cart (ParvoMedics Corporation, Sandy, Utah). Subjects fasted for 8 to 12 hours before the test. Attainment of Vo_{2max} was affirmed when subjects met 3 of 4 criteria: plateau of oxygen uptake (defined as <50 ml/min increase with 1% increase in treadmill grade), attainment ± 10 beats/min of age-predicted maximal heart rate, volitional exhaustion (defined as a rating of perceived exertion ≥ 18), and a calculated respiratory exchange ratio >1.10.[14]

Subjects' daily physical activity levels at baseline were documented using the Paffenbarger Physical Activity Questionnaire.[15] Subjects reported their average hours of physical activity over the course of the week to identify hours of sedentary, light, moderate, and vigorous activities (question 8, Paffenbarger Physical Activity Questionnaire). Vigorous activities were defined as any strenuous sports, jogging, aerobic exercise, bicycling on hills, and similar activities. Moderate activities were defined as lighter sports, regular walking, golf, and house and yard work. Total hours of moderate to vigorous physical activity (MVPA) per week were used to examine the relation among 25(OH)D, cardiorespiratory fitness, and daily physical activity. Body weight was measured using a calibrated balance beam scale. Height was determined using a wall-mounted tape measure. Serum 25(OH)D, which measures combined serum vitamin D2 and D3 levels, was determined using blood collected at the first

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Table 1
Subject baseline characteristics (n = 200)

Variable	Total	Men (n = 92)	Women (n = 108)	p Value*
Maximal oxygen uptake (ml/kg/min)	34 ± 10.3	40 ± 9.1	30 ± 8.5	<0.01
Age (years)	40 ± 14.4	39 ± 15.2	42 ± 13.9	0.12
Serum 25-hydroxy vitamin D (ng/ml)	34 ± 13.3	33 ± 11.3	35 ± 14.6	0.44
Waist circumference (cm)	85 ± 13.7	92 ± 12.2	80 ± 11.9	<0.01
Body mass index (kg/m^2)	26 ± 5.1	27 ± 4.5	26 ± 5.3	0.01
Moderate to vigorous physical activity (hours/week)	37 ± 19	36 ± 17.0	38 ± 20.0	0.56
Season (serum 25-hydroxy vitamin D measurement)				0.7
Spring	71 (35%)	31 (34%)	40 (37%)	
Summer	53 (26%)	27 (29%)	26 (24%)	
Fall	30 (15%)	15 (16%)	15 (14%)	
Winter	46 (23%)	19 (21%)	27 (25%)	

Values are presented as mean ± SD or number (percentage).
* For gender difference.

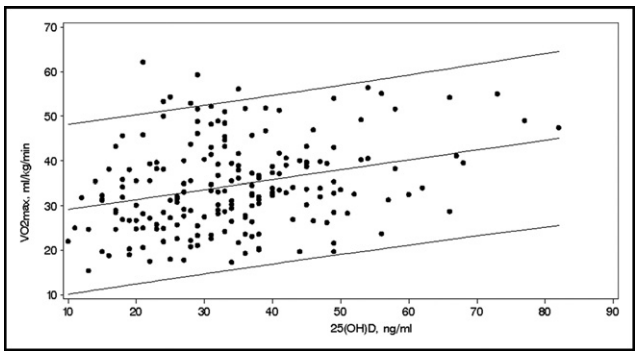

Figure 1. Simple linear regression equation and 95% prediction bands for regression of serum 25-hydroxy vitamin D with maximal oxygen uptake (n = 200, crude r = 0.29, p <0.0001).

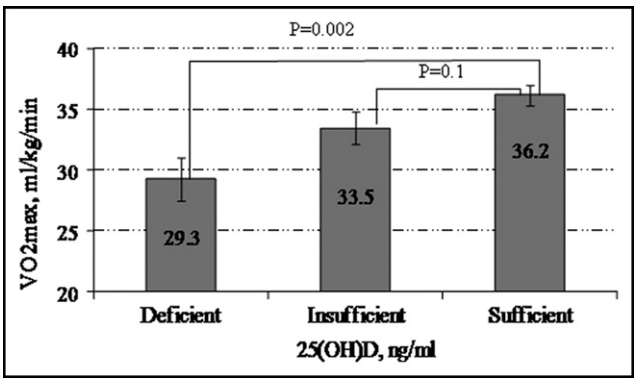

Figure 2. Comparison of mean maximal oxygen uptake (shown within bar graphs with corresponding SE) in subjects with deficient (≤20 ng/ml), insufficient (20 to 30 ng/ml), and sufficient (>30 ng/ml) 25-hydroxy vitamin D.

study visit using a standard enzyme-linked immunosorbent assay protocol (Clinical Laboratory Partners, Newington, Connecticut). The seasons in which the 25(OH)D level was measured were recorded to account for potential seasonal variation in 25(OH)D levels. The seasons were defined as winter (December to February), spring (March to May), summer (June to August), and fall (September to November).

The response variable of interest was cardiorespiratory fitness (Vo_{2max}). Independent variables included age, MVPA, 25(OH)D, body mass index (BMI), gender, cigarette smoking, and season. Means ± SDs were calculated for all continuous variables; frequencies and percentages were reported for all categorical variables. Bivariable associations were assessed using simple linear regression and *t* tests. Analysis of covariance was used to evaluate the relation between Vo_{2max} and serum 25(OH)D level after controlling for clinically and statistically significant predictors. Two-way interactions between predictors were considered in our analysis of covariance models. All analyses were performed using SAS 9.1.3 (SAS Institute, Cary, North Carolina).

Results

Data from 200 healthy adults were analyzed, of whom 108 (54%) were women and 22 (11%) were long-term smokers (Table 1). 25(OH)D levels were directly related to Vo_{2max} (r = 0.29, p <0.0001; Figure 1). Vo_{2max} was also significantly correlated with age (r = −0.58, p <0.0001) and BMI (r = -0.24, p = 0.0005). We also compared mean Vo_{2max} levels among 25(OH)D-deficient (≤20 ng/ml, n = 29, 15%), 25(OH)D-insufficient (20 to 30 ng/ml, n = 52, 26%), and 25(OH)D-sufficient (>30 ng/ml, n = 119, 59%) groups and documented higher Vo_{2max} values in the 25(OH)D-sufficient group (Figure 2).[7,8] The relation between 25(OH)D level and Vo_{2max} remained statistically significant even after adjusting for gender (p = 0.001), age (p = 0.0001), BMI (p = 0.0001), and MVPA (p = 0.05). Seasonal variation (p = 0.7) and tobacco use (p = 0.2) were not significantly associated with Vo_{2max}. There was also a statistically significant interaction between 25(OH)D level and MVPA (p <0.02), indicating that the effect of 25(OH)D level on Vo_{2max} is modified by hours of MVPA. Consequently, we reanalyzed the effect of 25(OH)D on Vo_{2max} by percentiles of physical activity. Mean hours of MVPA at the 25th (<23 hours/week, n = 49), 25th to 75th (23 to 48 hours/week, n = 103), and 75th (>48 hours/week, n = 48) percentiles were 16, 35, and 64 hours/week, respectively. Including these mean values in the model showed that for each SD (13 U) increase in 25(OH)D, Vo_{2max} increased by

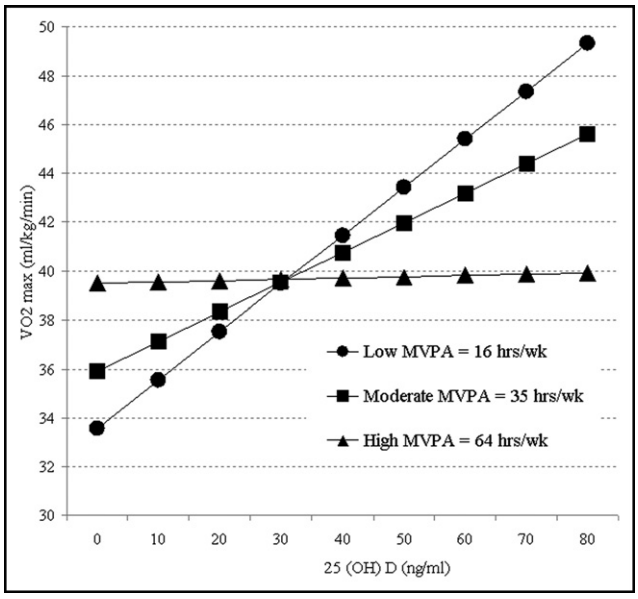

Figure 3. Relation between 25-hydroxy vitamin D and maximal oxygen uptake by percentiles and mean hours of moderate to vigorous physical activity for the low (25th percentile, 16 hours/week), moderate (25th to75th percentiles, 35 hours/week), and high (75th percentile, 64 hours/week) groups.

2.6 ml/kg/min ($p < 0.0001$) when MVPA was low, 1.6 ml/kg/min ($p < 0.0004$) when MVPA was moderate, and only 0.01 ml/kg/min ($p = 0.9$) when MVPA was high (Figure 3).

Discussion

This study is to our knowledge the first large cross sectional study of the relation between 25(OH)D levels and aerobic cardiorespiratory fitness. We documented that 25(OH)D is positively associated with cardiorespiratory fitness in healthy adults independent of their age, gender, and BMI. Moreover, this relation of 25(OH)D levels and aerobic exercise performance was more prominent in those subjects who did not engage in substantial amounts of MVPA.

There has been little published on the relation between cardiorespiratory fitness and serum 25(OH)D levels. Mowry et al[11] examined the association of baseline cardiorespiratory fitness (Vo_{2max}) with 25(OH)D in 59 young healthy women 16 to 24 years old. There was a positive association between Vo_{2max} and serum 25(OH)D ($r = 0.36$ $p < 0.05$). The present study confirms a direct relation between 25(OH)D levels and Vo_{2max} ($r = 0.29$, $p < 0.0001$) in men and women over a broad age range (20 to 73 years) and serum 25(OH)D levels (10 to 82 ng/ml). The positive relation between 25(OH)D levels and Vo_{2max} persisted after adjustment for age, gender, BMI, and MVPA, especially in subjects with low levels of physical activity. This suggests that 25(OH)D contributes to cardiorespiratory fitness.

An alternative explanation is that cardiorespiratory fitness is simply a surrogate for a subject's daily physical activity, which could be related to light exposure and therefore to 25(OH)D. To explore this hypothesis, we examined the interaction of MVPA and seasonal variation to the relation between 25(OH)D and Vo_{2max}. Despite the higher daily physical activity and serum 25(OH)D level observed during the warmer months, seasonal variations in 25(OH)D did not affect Vo_{2max} or the Vo_{2max}–25(OH)D relation.

We did find an interaction of 25(OH)D level with the amount of physical activity such that subjects with the lowest level of MVPA demonstrated the strongest relation between 25(OH)D and Vo_{2max}. For example, each SD increase in 25(OH)D level increased Vo_{2max} by 8% (with percent change calculated compared to the group average) in those with the lowest level of MVPA. Notably, this effect size is comparable to the change in Vo_{2max} observed with mild- to moderate-intensity exercise training.[16] One SD increase in serum 25(OH)D also increased Vo_{2max} by 5% in those with a moderate level of MVPA but only by 0.2% in those with a high level of MVPA (Figure 3).

The mechanism for the interactive effect of 25(OH)D and MVPA on cardiorespiratory fitness is not clear. Vo_{2max} is limited by cardiac output, arterial oxygen content, shunting of blood to active muscle, and extraction of oxygen by these muscles. Low serum 25(OH)D levels can cause myocardial hypertrophy, increased blood pressure, and endothelial dysfunction by 25(OH)D receptors[7,8,17–19] Consequently, low 25(OH)D levels may decrease cardiac output and increase peripheral vessel resistance, decreasing Vo_{2max}. Physical activity is also known to increase Vo_{2max} through increased cardiac output.[16,20,21] Results from a large healthy adult cohort study have suggested that the greatest benefits of physical activity on cardiac remodeling occur at the lowest levels of reported physical activity.[22] Therefore, 25(OH)D could potentially have a greater benefit on cardiac remodeling and Vo_{2max} in subjects with low levels of physical activity than in those who already engage in high levels of activity. There is also evidence that physical inactivity[23,24] and 25(OH)D deficiency[25–27] can cause muscle atrophy and shift muscle fiber type from IIa to IIb. Therefore, subjects with the lowest level of physical activity may receive a greater aerobic benefit from increasing 25(OH)D levels by changes in muscle mass and fiber type than those who already engage in high levels of physical activity. Alternatively, less active subjects in our study had a higher BMI ($p < 0.007$) and a larger waist circumference ($p < 0.02$). This could indicate a clustering of other CV risk factors such as insulin resistance, high blood pressure, and arterial stiffness, which could augment the negative effect of low 25(OH)D on Vo_{2max} in sedentary subjects.[28]

There are several limitations to this study. We did not record the amount of 25(OH)D taken by supplemental or dietary means. However, serum 25(OH)D level is reflective of all vitamin D sources and is the benchmark for determining vitamin D status. In addition, other biomarkers related to vitamin D such as serum parathyroid hormone, calcium, and phosphorus levels were not analyzed and could contribute to the relation between exercise performance and 25(OH)D. Furthermore, physical activity was measured by self-report and subject to recall bias, although the Paffenbarger Questionnaire has been well validated.[29]

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