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 (VO2max) 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 VO2max (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, VO2max 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 VO2max 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)

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 STOMP 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 VO2max.13 VO2max and ventilatory threshold were determined using breath-by-breath analysis of expired gases with a Parvo- medics TrueOne 2400 metabolic cart (ParvoMedics Corporation, Sandy, Utah). Subjects fasted for 8 to 12 hours before the test. Attainment of VO2max 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
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\textsubscript{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\textsubscript{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\textsubscript{2max} (\( r = 0.29, p < 0.0001; \) Figure 1). VO\textsubscript{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\textsubscript{2max} levels among 25(OH)D-deficient (\( \leq 20 \) 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\textsubscript{2max} values in the 25(OH)D-sufficient group (Figure 2). The relation between 25(OH)D level and VO\textsubscript{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\textsubscript{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\textsubscript{2max} is modified by hours of MVPA. Consequently, we reanalyzed the effect of 25(OH)D on VO\textsubscript{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\textsubscript{2max} increased by

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**Table 1**

Subject baseline characteristics (\( n = 200 \))

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

Values are presented as mean ± SD or number (percentage).
* For gender difference.
between VO2max and serum 25(OH)D (r
women 16 to 24 years old. There was a positive association
25(OH)D levels and VO2max (r
The present study confirms a direct relation between
laboratory fitness (VO2max) with 25(OH)D in 59 young healthy
subjects. This suggests that 25(OH)D contributes to cardiorespiratory fitness. We documented that
25(OH)D is positively associated with cardiorespiratory fit-
tness in healthy adults independent of their age, gender, and
BMI. Moreover, this relation of 25(OH)D levels and aerobic
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 al11 examined the association of baseline cardiorespira-
tory fitness (VO2max) with 25(OH)D in 59 young healthy
women 16 to 24 years old. There was a positive association
between VO2max and serum 25(OH)D (r = 0.36 p <0.05).
The present study confirms a direct relation between
25(OH)D levels and VO2max (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 rela-
tion between 25(OH)D levels and VO2max 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 fit-
tness is simply a surrogate for a subject’s daily physical
activity, which could be related to light exposure and there-
fore 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 VO2max. 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 VO2max or the VO2max–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 VO2max. For example, each SD in-
crease in 25(OH)D level increased VO2max 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 VO2max observed with
mild- to moderate-intensity exercise training.16 One SD
increase in serum 25(OH)D also increased VO2max 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. VO2max
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 pres-
sure, and endothelial dysfunction by 25(OH)D recep-
tors. Consequently, low 25(OH)D levels may de-
crease cardiac output and increase peripheral vessel
resistance, decreasing VO2max. Physical activity is also
known to increase VO2max through increased cardiac out-
put.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 VO2max
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 inactivity23,24 and 25(OH)D defi-
ciency25–27 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 mus-
cle 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 VO2max 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 reflec-
tive of all vitamin D sources and is the benchmark for
determining vitamin D status. In addition, other biomark-
ers related to vitamin D such as serum parathyroid hor-
mone, calcium, and phosphorus levels were not analyzed
and could contribute to the relation between exercise
performance and 25(OH)D. Furthermore, physical activ-
ity was measured by self-report and subject to recall bias,
although the Paffenbarger Questionnaire has been well
validated.29

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 to 75th
percentiles, 35 hours/week), and high (75th percentile, 64 hours/week)
groups.

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 fit-
ess 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.

An alternative explanation is that cardiorespiratory fit-
tness is simply a surrogate for a subject’s daily physical
activity, which could be related to light exposure and there-
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