Cardiorespiratory Fitness Is Independently Associated with 25-Hydroxyvitamin D in Chronic Kidney Disease

William G. Petchey,* Erin J. Howden,† David W. Johnson,*† Carmel M. Hawley,*† Thomas Marwick,† and Nicole M. Isbel*†

Summary
Background and objectives Vitamin D is an established important contributor to muscle function and aerobic metabolism. Hypovitaminosis D is highly prevalent in CKD patients and is associated with increased cardiovascular (CV) mortality via unknown mechanisms. Because aerobic-exercise capacity strongly predicts future CV events, we hypothesized that vitamin D status could be linked to CV outcomes via an effect on maximum aerobic-exercise capacity in patients with CKD and that this effect may be mediated in part via its actions on muscle strength and functional ability.

Design, setting, participants, & measurements Baseline demographic, anthropometric, and biochemical data were collected in a cross-sectional study of patients with moderate CKD. Peak aerobic capacity was determined during treadmill stress testing using metabolic equivalence of tasks. Physical activity was assessed using the Active Australia questionnaire, grip strength by dynamometer, and functional capacity by "Up & Go" testing.

Results The study included 85 participants (age 59.5 ± 9.7 years, 60% male, 44% diabetic, 92% Caucasian; mean serum 25-hydroxyvitamin D [25-OHD] 78.4 ± 29.4 nmol/L). We demonstrated that 25-OHD status was independently associated with aerobic-exercise capacity (β = 0.2; P = 0.008). Aerobic-exercise capacity was also predicted by younger age, white race, smaller waist circumference, absence of a previous angina history, and increasing weekly physical activity. However, neither muscle strength nor functional ability were significantly associated with 25-OHD.

Conclusions Vitamin D is independently associated with aerobic capacity in CKD patients, and this finding is not explained by changes in muscle strength or functional ability.


Introduction Patients with chronic kidney disease (CKD) suffer higher cardiovascular morbidity and mortality rates than the general population. Although traditional Framingham risk factors are common in this group, they do not fully explain the degree of cardiovascular disease encountered. Nontraditional factors, such as vitamin D status, have been shown to be highly correlated with mortality and morbidity in CKD stages 2 to 5 (1–4). However, the mechanisms underlying this association are unclear.

One way vitamin D status could affect cardiovascular (CV) outcomes is via its role in muscle strength, function, and aerobic capacity. Aerobic capacity (quantified clinically as cardiorespiratory fitness) is a strong prognosticator of cardiovascular outcomes, in terms of both morbidity and mortality (5–8). Animal studies have demonstrated the importance of vitamin D to muscle structure, function, and aerobic metabolism as a result of production of mitochondrial proteins, throughout of oxidative phosphorylation, and generation of ATP (9–12). Studies in the general population have shown strong correlations between vitamin D and both fall risk (13–15) and functional ability (16,17). Smaller studies in CKD populations, where hypovitaminosis is highly prevalent (18), have demonstrated similar associations of vitamin D with muscle strength and function (19–22). Given that vitamin D has a known role in muscle function and aerobic metabolism, we therefore hypothesized that serum 25-hydroxyvitamin D (25-OHD) will be independently associated with muscle strength, physical functional capacity, and peak aerobic capacity during exercise in patients with CKD stage 3 to 4.

Materials and Methods
Study Design All of the patients aged 18 or over with an Estimated GFR (eGFR) of 25–60 ml/min per 1.73 m² attending the outpatient department of Princess Alexandra Hospital Renal Unit (Brisbane, Australia) were invited to participate. These patients were recruited as part of the ongoing open-label randomized controlled trial LAND-
Mark 3. The study protocol was approved by the Princess
Alexandra Human Research Ethics Committee (HREC 2007/190) and was registered at www.anzctr.org.au (Registration
Number ANZCTR12608000337370). All of the participants
provided written informed consent. To establish the degree to
which these patients were representative of the overall gen-
eral nephrology outpatients, data were drawn from the Ne-
phrology Integrated Database. After assessment, those pa-
tients found to have serum 25-OHD concentrations <75
nmol/L were offered cholecalciferol supplementation as per
standard practice.

Demographic Data
Demographic and clinical data were recorded at the
study visit. Drug history, including both prescribed and
nonprescribed medications, was obtained. Use but not
quantity of 25-OHD precursor (ergocalciferol and cholecal-
ciferol) containing supplements was noted. Patients were
asked to cease β-blocker and nondihydropyridine calcium
channel blocker medications 48 hours before their study
visit.

Biochemical Testing
Blood specimens were collected after a 10-hour overnight fast.
Serum concentrations of creatinine, creatine kinase, al-
bumin, alkaline phosphatase, calcium (corrected for al-
bumin as total calcium – ([Albumin-40]×0.02)), phos-
phate, parathyroid hormone (PTH), glucose, insulin,
HbA1c, C-reactive protein, hemoglobin, and lipids (total
cholesterol, LDLs, HDLs, VLDLs, and triglycerides)
determined using standard automated techniques.

Serum 25-OHD was calculated using the MDRD-175 formula (23).
Insulin resistance was quantified using the Homeostatic
model assessment of insulin resistance formula (HOMA-IR),
calculated as ([glucose]×[insulin])/22.5 (24).

Serum 25-OHD was measured using Waters Acquity
Ultra Performance LC system, coupled with a Waters
Micromass Quatro Premier Mass Spectrometer (CV 7.6% at
76 nmol/L, lower limit of detection at <2 nmol/L). Vitamin
D status according to serum 25-OHD levels was
categorized as sufficient (>75 nmol/L), insufficient (38
to 74 nmol/L), or deficient (<37 nmol/L) as per Na-

dional Kidney Foundation Kidney Disease Outcomes
Quality Initiative guidelines (25). 1,25-Dihydroxyvitamin
D (1,25-OHD) was measured using Diasorin 2-step
RIA Kits (CV 15.9% at 69 pmol/L, lower limit of detect-
ton at <10 pmol/L).

Physical Assessment
During the same visit, patients had anthropometric as-
sessment, including height (meters), weight (kilograms),
and waist and hip circumference (centimeters). Body mass
index (BMI) was calculated as weight divided by height
squared. BP was taken as the 24-hour average from ambu-
latory monitoring (A&D TM-2430) during the day after the
initial baseline visit. Hand-grip strength was taken as the
maximum kilograms of force of three attempts per hand,
using a dynamometer (TMT, Tokyo, Japan). Physical-activity
levels were assessed using the validated Active Aus-
tralia Questionnaire (26,27), with the total weekly time
(minutes) spent doing health-enhancing physical activity cal-
culated as [time spent continuously walking >10 minutes +
time spent in moderate activity + (2×time spent in vigorous
activity)], with individuals achieving greater than 1680 min/wk
recorded to 1680 minutes to prevent errors in over-reporting.
Functional capacity was assessed by the timed “Up & Go” test,
in which participants were timed standing from a seated posi-
tion, walking 3 meters, turning 180 degrees, walking back
sitting (28). The quickest time of three attempts was used for
analysis. For assessment of endurance and fitness, patients also
completed a 6-minute walk test, with distance achieved in met-
ers as the outcome (29).

Exercise Testing
Participants completed a Duke Activity Status Index (30) to
assess likely aerobic capacity. On the basis of these results, a
suitable protocol was selected (Bruce, Naughton, Balke, or
modified Balke), and participants completed a treadmill
stress test. Testing was terminated at symptom limitation
(angina, dyspnoea, or fatigue) or the development of adverse
signs (hypotension, dysrhythmia, or significant ST segment
development). Heart rate and BP were monitored. A 12-lead
electrocardiogram was recorded before exercise, serially
throughout testing, and at 1-minute intervals during recov-
ery. Metabolic equivalents of task (METs) achieved during
exercise, estimates of peak total-body oxygen consumption
for a given workload (31), were calculated from the speed
and gradient of the treadmill at peak exercise and expressed
as a multiple of the assumed basal oxygen consumption at
rest of 3.5 ml/kg of body weight/min (32).

Statistical Methods
The data were assessed for normality of distribution and
transformed, as appropriate. Because no suitable transformation
was found for weekly physical activity, the data were converted
into ordinal categories of 300 minutes blocks. The results were
expressed as the means ± SD for continuous normally distrib-
uted data, median (interquartile range [IQR]) for continuous,
normally distributed data, and frequency (%) for
categorical data. Comparisons of means for independent
samples were made using unpaired t test or ANOVA for
normally distributed data, Mann-Whitney or Kruskall-Wallis
test for non-normally distributed data, and either Fisher’s exact
test or Pearson’s chi-squared test for categorical data. The degree
of association between 25-OHD and the variables of interest
were assessed using Pearson’s correlation for continuous nor-
mally distributed variables and Spearman’s correlation for cat-
egorical or non-normally distributed data. Linear regression
was performed, as appropriate, and standard-regression diagnostics
were performed. Multivariate models were constructed using
stepwise backward regression. The null hypothesis was rejected
at the 0.05 level. All of the statistical analyses were performed
using Stata Version 11.1.

Results
Participant Characteristics
Eighty-five patients were recruited between March 1, 2008,
and February 1, 2010. The baseline characteristics of the study
population are presented in Table 1. Compared with the
general nephrology outpatient population, the cohort was of
similar age (59.5 ± 9.7 versus 60.7 ± 16.4 years, P = 0.52), sex
(55.9 versus 60% male, P = 0.5), and diabetic status (43.5 versus

Demographic Table 1. Baseline characteristics of the group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cohort (n = 85)</th>
<th>Tertiles of 25-OHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lowest (≤59 nmol/L)</td>
</tr>
<tr>
<td></td>
<td>(n = 29)</td>
<td>(n = 28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age (years)</td>
<td>59.5 ± 9.7</td>
<td>57.2 ± 10.7</td>
</tr>
<tr>
<td>male (%)</td>
<td>51 (60)</td>
<td>15 (52)</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>78 (92)</td>
<td>24 (83)</td>
</tr>
<tr>
<td>diabetics (%)</td>
<td>37 (44)</td>
<td>18 (62)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.2 ± 7.3</td>
<td>35.1 ± 8.6</td>
</tr>
<tr>
<td>25-OHD precursor use (%)</td>
<td>14 (16)</td>
<td>3 (10)</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemoglobin (g/L)</td>
<td>133 ± 16</td>
<td>131 ± 17</td>
</tr>
<tr>
<td>bicarbonate (mmol/L)</td>
<td>25.6 ± 2.8</td>
<td>24.7 ± 3.2</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>39.0 ± 9.3</td>
<td>39.1 ± 9.6</td>
</tr>
<tr>
<td>urinary protein:creatinine (g/mol)</td>
<td>40 (14 to 104)</td>
<td>59 (18 to 173)</td>
</tr>
<tr>
<td><strong>Cause of renal disease (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diabetes</td>
<td>22 (26)</td>
<td>10 (35)</td>
</tr>
<tr>
<td>renovascular</td>
<td>6 (7)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>glomerulonephritis</td>
<td>6 (7)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>other</td>
<td>51 (60)</td>
<td>15 (52)</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>current smoker (%)</td>
<td>12 (14)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>previous coronary event (%)</td>
<td>26 (31)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>total cholesterol (mmol/L)</td>
<td>4.5 ± 1.1</td>
<td>4.6 ± 1.3</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>2.5 ± 0.9</td>
<td>2.4 ± 0.9</td>
</tr>
<tr>
<td>systolic blood pressure (mmHg)</td>
<td>136 ± 21</td>
<td>137 ± 22</td>
</tr>
<tr>
<td>diastolic blood pressure (mmHg)</td>
<td>81 ± 12</td>
<td>80 ± 14</td>
</tr>
<tr>
<td><strong>Bone mineral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>corrected calcium (mmol/L)</td>
<td>2.38 ± 0.18</td>
<td>2.37 ± 0.08</td>
</tr>
<tr>
<td>phosphate (mmol/L)</td>
<td>1.12 ± 0.20</td>
<td>1.18 ± 0.23</td>
</tr>
<tr>
<td>parathyroid hormone (pmol/L)</td>
<td>9.5 (7 to 14)</td>
<td>11 (8 to 16)</td>
</tr>
<tr>
<td>25-OHD (nmol/L)</td>
<td>78.4 ± 29.4</td>
<td>46.4 ± 11.3</td>
</tr>
<tr>
<td>1,25-OHD (pmol/L)</td>
<td>91.5 ± 46.1</td>
<td>73.9 ± 28.9</td>
</tr>
</tbody>
</table>

*Between groups.

35.7% diabetic, P = 0.2). However, the study group had significantly higher BMIs (33.2 ± 7.4 versus 30 ± 7.6 kg/m², P = 0.0003), and a higher percentage were Caucasian (91.8 versus 80.5%, P = 0.01).

The mean 25-OHD level was 78.4 ± 29.4 nmol/L. Half (48%) were vitamin D sufficient, whereas the remainder were either insufficient (45%) or deficient (7%). One patient took prescribed cholecalciferol, and 14 patients (16.5%) in total took 25-OHD precursors. There was no significant difference in demographic or physical characteristics between those supplemented and those not, and 25-OHD levels were similar regardless (86.9 ± 30.9 versus 76.7 ± 29.1 nmol/L, P = 0.2).

Physical and Anthropometric Results

The majority of participants were obese with a mean BMI of 33.2 ± 7.4 kg/m². The adverse metabolic phenotype was highlighted by the propensity to central obesity with average waist circumferences of 110.6 ± 17.8 cm (men) and 103.3 ± 17.8 cm (women). On univariate analysis, neither maximum grip strength nor functional capacity (quickest “Up & Go” time) was correlated with serum 25-OHD (r = 0.17, P = 0.1; rho = −0.17, P = 0.13, respectively). Self-reported time spent in health-enhancing physical activity per week was significantly positively correlated with 25-OHD (rho = 0.41, P < 0.0001), as was distance achieved during the 6-minute walk test (r = 0.25, P = 0.02).

Predictors of Vitamin D Status

Using simple bivariate regression, higher serum 25-OHD concentrations were predicted by Caucasian race (r² = 0.068, P = 0.016), absence of diabetes (r² = 0.071, P = 0.01), higher serum albumin (r² = 0.075, P = 0.01), lower fasting blood glucose (r² = 0.118, P = 0.001), lower HOMA-IR score (r² = 0.10, P = 0.003), lower HbA1c (r² = 0.106, P = 0.002), and higher levels of weekly physical activity (r² = 0.15, P = 0.0003). Serum 25-OHD was higher in patients recruited during the summer (December through February, 83.2 ± 32.3 nmol/L) and autumn (March through May, 89.9 ± 28.2 nmol/L) compared with winter (June through August, 71.5 ± 27.0 nmol/L) and spring (September through November, 73.2 ± 28.8 nmol/L). However, this difference was not statistically significant (F [3,81] = 1.79, P = 0.2). Neither BMI nor eGFR was correlated with 25-OHD levels (rho = −0.13, P = 0.23; r = 0.074, P = 0.5, respectively).
Association of Vitamin D with Traditional Cardiovascular Risk Factors

To assess the association of 25-OHD with traditional cardiovascular risk factors, patients were divided into 25-OHD tertiles. Compared with the highest tertile (25-OHD ≥ 96 nmol/L), more patients in the lowest tertile (25-OHD ≤ 59 nmol/L) were diabetic (62 versus 32%, P = 0.023). Even if patients with diabetes were excluded, those in the lowest tertile were significantly more insulin resistant compared with those in the highest tertile (HOMA-IR 5.78 ± 5.95 versus 2.69 ± 2.01, P = 0.046). There were no differences in cardiovascular risk factors between groups otherwise (Table 1).

Exercise-3 Treadmill Testing

Eighty-one patients completed exercise treadmill testing (Table 2). The remaining four patients had mobility-limiting osteoarthritis (n = 3) or declined stress testing (n = 1). Median time on treadmill was 7.1 minutes (IQR 5.2 to 9.3). The average maximum heart rate of participants was 91.9 ± 13.4% of age-predicted maximum, with 73.2% achieving a heart rate >85% of age-predicted maximum. Peak aerobic capacity achieved during exercise stress testing was 6.2 METs (IQR 4.6 to 8.7). Both percentage of age-predicted heart rate maximum achieved and log10(METs) were significantly associated with 25-OHD (r = 0.24, P = 0.03; r = 0.29, P = 0.008, respectively; Figure 1).

Associations with Peak Aerobic Capacity (METs)

Univariate associations with peak METs achieved are summarized in Table 3. Upon reviewing METs achieved by tertiles of vitamin D, there was a significant difference between those in the lowest tertile compared with those in the highest tertile (4.95 [3.7 to 7.0] versus 6.8 [4.9 to 10.2], P = 0.01). Using stepwise regression, METs achieved during exercise were independently predicted by younger age, Caucasian race, smaller waist circumference, no history of angina, and more physical activity performed per week (n = 79, adjusted R² = 0.48, P < 0.0001; two patients had incomplete Active Australia questionnaires, so were excluded from model). The addition of 25-OHD to this model demonstrated a significant independent incremental improvement in model fit (model adjusted R² = 0.53, P < 0.0001; semipartial R² = 0.046, P = 0.008). The association of 25-OHD with log10(METs) was independent of the bone mineral biochemical parameters, calcium, phosphate, PTH, and 1,25-OHD (Table 4).

Discussion

This study demonstrated an independent association between vitamin D status and peak aerobic capacity achieved during exercise testing among patients with CKD stages 3 to 4. This correlation with cardiorespiratory fitness was also supported by the finding of a significant relationship between vitamin D status and distance achieved during the 6-minute walk test. No relationship was demonstrated within this patient group between vitamin D and muscle strength or functional capacity.

These findings are in keeping with those of Mowry et al. (33), who reported a significant correlation (r = 0.36, P < 0.05) between 25-OHD levels and cardiorespiratory fitness, determined by VO2 max, in healthy young women aged 16 to 24 years. Furthermore, Mowry et al. similarly observed an association between aerobic capacity and adiposity, manifest as waist circumference and BMI, both of which are also known to strongly predict future cardiovascular events (34).

The fact that 25-OHD’s association with METs was independent of calcium, phosphate, and PTH is not surprising because the extraosseous role of vitamin D is well described (35). Indeed, considering extraskeletal explanations of vitamin D’s role in aerobic metabolism, it may be that muscle and cardiac mitochondrial function and oxygen consumption are factors. Cardiac myocytes possess the vitamin D receptor (36) and have vitamin D-dependent oxidative phosphorylation, such that ATP production is reduced in states of hypovitaminosis D to levels that are 25% lower than controls (10).

It is important to note that this study demonstrated an association of vitamin D with peak METs that was independent of physical activity and improved the fit of the explanatory multivariate model by approximately 5%. Physical activity and cardiorespiratory fitness have recently been uncoupled as cardiovascular risks and stand independently of each other, despite the ability of vigorous activity to improve aerobic capacity (37). Compared with a sedentary lifestyle, participation in any physical activity has been shown to be associated with a better vitamin D status, both in this study

Table 2. Treadmill stress test parameters and correlation with serum 25-hydroxyvitamin D levels

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Participants (n = 81)</th>
<th>r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate max (bpm)</td>
<td>147.1 ± 21.9</td>
<td>0.18</td>
<td>0.1</td>
</tr>
<tr>
<td>Heart rate max (% age predicted max)a</td>
<td>91.9 ± 13.4</td>
<td>0.24</td>
<td>0.03</td>
</tr>
<tr>
<td>Blood pressure max</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic (mmHg)</td>
<td>183.9 ± 23.3</td>
<td>0.008</td>
<td>0.9</td>
</tr>
<tr>
<td>diastolic (mmHg)</td>
<td>83.3 ± 12.7</td>
<td>0.08</td>
<td>0.5</td>
</tr>
<tr>
<td>peak aerobic capacity (METs)b</td>
<td>6.2 (4.6 to 8.7)</td>
<td>0.29</td>
<td>0.008</td>
</tr>
</tbody>
</table>

aAge predicted heart rate max = (220 – age [years]).
bLog10 transformed for analysis.
and that of Scragg et al. (38). Consequently, the independent correlation of 25-OHD and achieved METs suggests that future exploration of a more mechanistic role for vitamin D in aerobic capacity is warranted.

The lack of association between muscle strength and serum 25-hydroxyvitamin D status was surprising. Use of hand-grip strength was based on the assumption that the results achieved were representative of total-body strength (39), but a recent factorial analysis has demonstrated that although force measured by hand dynamometer is representative of upper-limb strength, it may not be representative of lower-limb or total-body strength (40). However, Stewart et al. (41) demonstrated a significant association between grip strength and 25-hydroxyvitamin D status, albeit in the non-CKD population, but with 242 participants, 19.4% of whom had 25-OHD levels of <50 nmol/L. Therefore, the apparent disparity in results may be due to the effect of modification by the presence of CKD or alternatively by the range of 25-OHD encountered in the study population.

This assertion is further supported by the lack of association of vitamin D with the “Up & Go” test; osteomalacia is known to principally effect muscles of the lower limb and trunk (42–44), and previous studies have correlated hypovitaminosis D with weakness of the lower-limb musculature (16,45). Despite the “Up & Go” test being primarily a test of gait and functional capacity, it is anatomically reliant on the proximal muscle groups of the lower limb and as such would be expected to correlate with 25-OHD, as proven by functional assessment of lower-limb proximal muscle groups in previous studies (16,46,47). All of these studies divided the study cohort by vitamin D status, and the maximal improvement in lower-limb function was observed between those in the most deficient groups (<50, <40, and <30 nmol/L, respectively) and the rest of the cohort. A recent review ana-

| Table 3. Univariate and multivariate associations with peak aerobic capacity (log10[METs]) |
| Variable | Univariate Analysis (n = 85) | Multivariate Model (n = 79, adjusted R² = 0.53, P < 0.0001) |
| | Coefficient | P | Coefficient | 95% Confidence Interval | Standardized β Weight | P |
| Age (years) | -0.27 | 0.01 | -0.34 | -0.771 to 0.012 | <0.0001 |
| Sex | 0.4 | 0.0001 | 0.3 | -0.420 to 0.033 | 0.001 |
| Race (Caucasian/other) | 0.0006 | 0.7 |
| Diabetes | -0.30 | 0.006 | -0.3 | 0.008 |
| Smoking status (current) | 0.03 | 0.0002 |
| BMI (kg/m²) | -0.21 | 0.06 | 0.0 | 0.008 |
| Waist circumference (cm) | -0.29 | 0.0008 | 0.0 |
| Hip circumference (cm) | -0.29 | 0.0008 |
| Waist:hip ratio | 0.03 | -0.28 | 0.01 |
| History of angina | 0.05 | 0.001 |
| History of PVD | 0.01 |
| History of dyslipidaemia | 0.01 |
| Hemoglobin (g/L) | 0.26 | 0.002 | -0.2 | 0.008 |
| Hematocrit | 0.21 | 0.06 |
| Creatine kinase (U/L) | -0.04 | 0.8 |
| Alkaline phosphatase (U/L) | -0.03 | 0.8 |
| Corrected calcium (mmol/L) | -0.20 | 0.07 |
| Phosphate (mmol/L) | -0.29 | 0.008 | 0.2 | 0.008 |
| 25-Hydroxyvitamin D (nmol/L) | 0.29 | 0.008 | 0.2 |
| 1,25-Dihydroxyvitamin D (pmol/L) | 0.19 | 0.09 |
| PTH (pmol/L) | -0.06 | 0.6 | 0.2 |
| Maximum grip strength (kg force) | 0.26 | 0.02 | 0.2 |
| HEPA minutes/wk | 0.2 |

HEPA, health-enhancing physical activity; PVD, peripheral vascular disease.

| Table 4. Bone mineral homeostasis markers in relation to peak METs achieved |
| Variable | Multivariate Model (log10[METs]; n = 80, adjusted R² = 0.15, P = 0.005) |
| | Coefficient | 95% Confidence Interval | β | P |
| Corrected calcium | -0.380 | -0.771 to 0.012 | -0.24 | 0.06 |
| Phosphate | -0.194 | -0.420 to 0.033 | -0.19 | 0.1 |
| Parathyroid hormone | 0.001 | -0.004 to 0.006 | 0.06 | 0.6 |
| 25-Hydroxyvitamin D | 0.001 | -0.000 to 0.003 | 0.21 | 0.05 |
| 1,25-Dihydroxyvitamin D | 0.001 | -0.000 to 0.002 | 0.21 | 0.1 |

... and that of Scragg et al. (38). Consequently, the independent correlation of 25-OHD and achieved METs suggests that future exploration of a more mechanistic role for vitamin D in aerobic capacity is warranted.
alyzed optimal serum 25-OHD concentrations for lower-limb muscle function from meta-analysis of the available data and found that the majority of correlation and improvement in muscle strength and function came with increasing serum 25-OHD levels up to 40 nmol/L. Serum 25-OHD concentrations ≥40 nmol/L demonstrated a much more modest correlation with muscle strength. Because only seven patients (8.24%) of our cohort had serum 25-OHD levels <40 nmol/L, we may also not have had the spectrum of vitamin D deficiency where muscle strength would be demonstrably diminished or indeed large enough numbers to discern a more subtle relationship with improvements in muscle strength above this level.

The limitations of this study were the relatively small size of the population sampled and its cross-sectional design. The fact that the population recruited was entered into a randomized controlled trial may have introduced ascertainment bias, both in terms of entrance criteria for the study and personal motivation to participate. However, the characteristics of the study group did not differ appreciably from those of the general nephrology population. Even though the season of the baseline visit and local UV indices were known, individual exposure to available sunlight was unable to be taken into account. Additionally, there were not the levels of hypovitaminosis D encountered that were expected, probably in part because of the over-representation of Caucasian participants together with the relatively high UV index of Brisbane, Australia. Finally, the demonstration of association between serum 25-OHD levels and cardiorespiratory fitness does not establish a cause and effect relationship. A randomized controlled trial examining the impact of physical training, vitamin D supplementation, or a combination of both on peak cardiorespiratory fitness is required.

Conclusions

In conclusion, vitamin D is independently associated with cardiorespiratory fitness in CKD patients, and this finding is not explained by changes in muscle strength or functional ability. Although the results should be considered preliminary, they provide an important insight into vitamin D’s extraskeletal actions and should prompt further study of aerobic capacity as a possible mediator explaining the relationship between vitamin D and cardiovascular outcomes in CKD.

Acknowledgments

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Disclosures

None.

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