Relationship Between Serum 25-Hydroxyvitamin D and Pulmonary Function in the Third National Health and Nutrition Examination Survey*

Peter N. Black, MB ChB; and Robert Scragg, MB BS, PhD

Context: Age, gender, height, ethnicity, and smoking are important determinants of lung function but do not explain all of the variation between individuals. Low concentrations of vitamin D have been associated with a number of diseases, including osteoporosis, hypertension, and type I diabetes. It is possible that serum concentrations of vitamin D might also influence pulmonary function.

Objectives: To determine the relationship between serum concentrations of 25-hydroxy vitamin D and pulmonary function.

Design, setting, and participants: The analysis was conducted using data from the Third National Health and Nutrition Examination Survey, which was a cross-sectional survey of the US civilian population that was conducted from 1988 to 1994. The analyses were restricted to 14,091 people who ≥ 20 years of age, were interviewed at mobile examination centers, and had undergone spirometry, and in whom serum 25-hydroxy vitamin D levels had been measured.

Results: After adjustment for age, gender, height, body mass index, ethnicity, and smoking history, the mean FEV₁ was 126 mL (SE, 22 mL), and the mean FVC was 172 mL (SE, 26 mL) greater for the highest quintile of serum 25-hydroxy vitamin D level (≥ 85.7 nmol/L) compared with the lowest quintile (≤ 40.4 nmol/L; p < 0.0001). With further adjustment for physical activity, the intake of vitamin D supplements, milk intake, and the level of serum antioxidants, the mean difference between the highest and lowest quintiles of 25-hydroxy vitamin D was 106 mL (SE, 24 mL) for FEV₁, and 142 mL (SE, 29 mL) for FVC (p < 0.0001).

Conclusions: There is a strong relationship between serum concentrations of 25-hydroxy vitamin D, FEV₁, and FVC. Further studies are necessary to determine whether supplementation with vitamin D is of any benefit in patients with respiratory disease.

(CHEST 2005; 128:3792–3798)

Key words: FEV₁; FVC; pulmonary function; Third National Health and Nutrition Examination Survey; vitamin D

Abbreviations: BMI = body mass index; MET = metabolic equivalent; NHANES III = Third National Health and Nutrition Examination Survey

Age, height, and gender are important determinants of pulmonary function,¹² and cigarette smoking is recognized as an important cause of impaired lung function.³⁴ There is also evidence that diet can influence FEV₁ and vital capacity. Individuals with a high intake of fruit have a higher FEV₁ and fewer respiratory symptoms than those who eat fruit infrequently.⁵⁻⁸ In keeping with this, both the

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The authors have received funding from the Health Research Council of New Zealand.

Manuscript received May 14, 2005; revision accepted July 23, 2005.

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Clinical Investigations
Low concentrations of vitamin D have been linked to many diseases including osteoporosis, hypertension, ischemic heart disease, type I diabetes, and cancer. The effects of supplementation with vitamin D on fractures also have been studied, although the results have been conflicting. Some studies have suggested a reduction in osteoporotic fractures, although a recent large study did not confirm this finding. Vitamin D is synthesized in the skin following sunlight exposure, but concentrations of vitamin D can also be influenced by dietary intake. Vitamin D is converted to 25-hydroxy vitamin D through the action of a hydroxylase in the liver, and this, in turn, is converted into 1,25-dihydroxyvitamin D, the active metabolite, in the kidney. 1,25-dihydroxy vitamin D has a number of actions that may be relevant to respiratory disease. It inhibits the formation of matrix metalloproteinases as well as fibroblast proliferation, and influences collagen synthesis; these actions mean that 1,25-dihydroxy vitamin D could influence tissue remodeling. These observations raise the possibility that vitamin D could influence lung function. The third National Health and Nutrition Examination Survey (NHANES III) provided the opportunity to examine the relationship between vitamin D status and lung function in a large sample that was representative of the US population.

Materials and Methods

A cross-sectional survey representative of the US civilian noninstitutionalized population (NHANES III) was carried out from 1988 to 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention. A stratified, multistage sampling design was used to recruit participants from household clusters, with oversampling of non-Hispanic blacks and Mexican Americans. After an initial interview at home, participants visited mobile centers where they underwent an extensive physical examination. The survey methods, including sampling, interview, examination and laboratory measurement of blood samples, ethical approval, and informed consent, have been published in more detail elsewhere. A total of 23,258 adults who were ≥20 years of age were invited to take part in the survey. Of these, 18,825 persons were interviewed at home, and of those, 16,573 persons attended mobile examination centers.

In the home interview, information was collected on a wide range of variables including age, sex, ethnicity (self-assigned as non-Hispanic white, non-Hispanic black, Mexican American, or Other), current cigarette smoking status, and history of ever having been told by a doctor or other health professional of having asthma, hay fever, emphysema, and chronic bronchitis. Information was also collected at the home interview on the following covariates: the frequency of intake of milk and supplements (including vitamin D) in the previous month; and the number of times a range of common physical activities were undertaken during leisure time in the previous month. Metabolic equivalents (METs) were assigned for each physical activity. Participants who were ≥60 years of age were classified as having moderate activity if the MET for any activity was ≥3.0, and were classified as having vigorous activity if the MET was ≥6.0. Those persons between the ages of 20 and 59 years were classified as having moderate activity if the MET for any activity was ≥3.5 or as having vigorous activity if the MET was ≥7.0.

At the mobile examination centers, participants were dressed in underpants, disposable light clothing, and slippers while being weighed on electronic scales, in kilograms, to two decimal places. Height was measured with a fixed stadiometer to the nearest millimeter. Body mass index (BMI) was calculated as the weight (in kilograms) divided by the square of height (in meters). Lung function was measured using a spirometer (Ohio 827 rolling seal spirometer; Ohio Medical Instrument Company, Cincinnati, Ohio). Spirometry was performed according to American Thoracic Society criteria. Participants were asked to perform five acceptable forced expiratory maneuvers. The FEV1 was recorded as the highest value obtained from the acceptable maneuvers.

Blood samples collected during the examination were centrifuged, aliquoted, and frozen to −70°C on site, and were shipped on dry ice to central laboratories where they were stored at −70°C until analysis. Serum concentrations of 25-hydroxyvitamin D were measured by a radioimmunoassay after extraction with acetonitrile. Serum 25-hydroxyvitamin D concentrations ranged from 8.7 to 243.6 nmol/L, not including one person with a concentration of 400.1 nmol/L. Serum samples were also analyzed for the antioxidants vitamin C, vitamin E, and beta-carotene by high-performance liquid chromatography, and for selenium by spectrophotometry. All of these antioxidants were associated with lung function in NHANES III, and are potential confounders of any association between vitamin D and lung function.

The data in this report are restricted to non-Hispanic white, non-Hispanic black, and Mexican-American adults ≥20 years of age who attended the mobile examination centers (n = 14,076). Participants who were of “other” ethnicity (n = 662) and those who had missing measurements for FEV1 (n = 1137), 25-hydroxyvitamin D (n = 616), or BMI (n = 15) were excluded from the study. Those who had missing information on their current status of cigarette smoking (n = 66) were also excluded as was one individual with a very high outlying 25-hydroxyvitamin D value of 400.1 nmol/L. Statistical analyses were carried out with a statistical software package (SUDAAN, version 9.0; RTI International; Research Triangle Park, NC), using the sampling weights for the mobile examination centers to adjust for the oversampling of non-Hispanic blacks and Mexican Americans, so that the data were representative of the US civilian noninstitutionalized population, and to correct SEs for any design effect arising from clustered sampling. A procedure (REGRESS) was used to estimate the adjusted means of continuous outcome variables (ie, serum 25-hydroxyvitamin D, FEV1, and FVC), with independent variables including quintile (ie, the portion of the frequency distribution containing one fifth of the total sample) of serum antioxidants and BMI entered as categoric variables (aside from height). The Wald F test was used to assess the dose response. Interaction
terms were created by multiplying serum 25-hydroxy vitamin D concentrations (as a continuous variable) with variables of interest (analyzed as dummy variables), and their β-coefficients were used to determine whether the associations between FEV₁ and 25-hydroxy vitamin D varied between subgroups.

RESULTS

The adjusted mean serum concentrations of 25-hydroxyvitamin D for the main covariates are shown in Table 1. The serum 25-hydroxyvitamin D concentration was higher in men than in women, was inversely related to BMI, and declined with age. It was also lower in non-Hispanic blacks and Mexican Americans compared with non-Hispanic whites, and it was lower in participants smoking > 20 cigarettes a day compared with nonsmokers.

Table 2 shows the mean (SE) FEV₁ by gender, age, ethnicity, BMI, cigarette smoking, and quintile of 25-hydroxyvitamin D level after adjusting for all of the other variables in the table. The mean difference in FEV₁ between the lowest and highest quintile of 25-hydroxyvitamin D concentration was 126 mL (SE, 22 mL). This compares with a mean adjusted difference for FEV₁ of 345 mL (SE, 24 mL) between individuals who had never smoked and those who were currently smoking ≥ 20 cigarettes per day.

The relationship between 25-hydroxyvitamin D level and FVC is also shown in Table 2. The findings are similar to those for FEV₁. Following adjustment for the same variables as for FEV₁, the difference in FVC between the lowest and highest quintile of 25-hydroxyvitamin D concentration was 172 mL (SE, 26 mL). There was, however, no difference in the FEV₁/FVC ratio between the lowest and highest quintile, and this was 0.78 in both groups. Inclusion of the single outlier with a very high 25-hydroxyvitamin D result did not change the mean values of FEV₁ and FVC for the highest quintile of vitamin D.

The effect of gender, age, ethnicity, cigarette smoking, and diagnoses of asthma, bronchitis, and emphysema on the relationship between FEV₁ and 25-hydroxyvitamin D level is shown in Table 3. The

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients, No.</th>
<th>Mean (SE)</th>
<th>Mean Difference (SE)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6,644</td>
<td>78.3 (0.9)</td>
<td>6.6 (0.8)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Female</td>
<td>7,432</td>
<td>71.7 (0.9)</td>
<td>0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>p Value for Wald F statistic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29 yr</td>
<td>3,016</td>
<td>81.3 (1.3)</td>
<td>0</td>
<td>0.026</td>
</tr>
<tr>
<td>30–39 yr</td>
<td>2,875</td>
<td>78.1 (1.5)</td>
<td>−3.1 (1.4)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>40–49 yr</td>
<td>2,254</td>
<td>73.1 (1.2)</td>
<td>−8.1 (1.3)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>50–59 yr</td>
<td>1,602</td>
<td>72.0 (0.9)</td>
<td>−9.2 (1.4)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>60–69 yr</td>
<td>1,953</td>
<td>70.0 (0.9)</td>
<td>−11.3 (1.6)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>≥ 70 yr</td>
<td>2,376</td>
<td>66.4 (0.9)</td>
<td>−14.8 (1.6)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>p Value for Wald F statistic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NH-white</td>
<td>6,153</td>
<td>79.2 (0.9)</td>
<td>0</td>
<td>&lt; 0.0001</td>
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<tr>
<td>NH-black</td>
<td>3,957</td>
<td>48.6 (1.2)</td>
<td>−30.6 (1.3)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Mex-Am</td>
<td>3,966</td>
<td>61.0 (1.0)</td>
<td>−18.2 (1.4)</td>
<td>&lt; 0.0001</td>
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<tr>
<td>p Value for Wald F statistic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI quintile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 22.4</td>
<td>2,789</td>
<td>80.1 (1.0)</td>
<td>0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>22.5–25.0</td>
<td>2,814</td>
<td>77.9 (1.2)</td>
<td>−2.2 (0.9)</td>
<td>0.027</td>
</tr>
<tr>
<td>25.1–27.6</td>
<td>2,871</td>
<td>75.0 (1.0)</td>
<td>−5.1 (1.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>27.7–31.1</td>
<td>2,758</td>
<td>72.7 (1.1)</td>
<td>−7.4 (0.9)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>≥ 31.2</td>
<td>2,844</td>
<td>66.0 (0.9)</td>
<td>−14.1 (1.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>p Value for Wald F statistic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 20/d</td>
<td>1,564</td>
<td>72.3 (1.1)</td>
<td>−3.1 (1.2)</td>
<td>0.013</td>
</tr>
<tr>
<td>10–19/d</td>
<td>955</td>
<td>72.2 (1.7)</td>
<td>−3.3 (1.7)</td>
<td>0.052</td>
</tr>
<tr>
<td>&lt; 10/d</td>
<td>1,124</td>
<td>73.6 (1.8)</td>
<td>−1.9 (1.9)</td>
<td>0.34</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>3,543</td>
<td>76.2 (1.2)</td>
<td>0.8 (0.9)</td>
<td>0.41</td>
</tr>
<tr>
<td>Never smoked</td>
<td>6,890</td>
<td>75.5 (1.0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>p Value for Wald F statistic</td>
<td></td>
<td></td>
<td></td>
<td>0.051</td>
</tr>
</tbody>
</table>

*NH = non-Hispanic; Mex-Am = Mexican American.
† By t test.
The association between 25-hydroxyvitamin D level and FEV₁ was seen in both non-Hispanic whites and non-Hispanic blacks but not for Mexican Americans, although when 25-hydroxyvitamin D level was analyzed as a continuous variable, its association with FEV₁ did not vary between Mexican Americans and either non-Hispanic whites (p = 0.24) or non-Hispanic blacks (p = 0.92). The association between FEV₁ and 25-hydroxyvitamin D was greater for those ≥ 60 years of age compared with those below this age, but on testing for an interaction between age and 25-hydroxyvitamin D level there was no significant effect (p = 0.12). In Table 3, the association between FEV₁ and 25-hydroxyvitamin D level appears to be greater among current smokers and ex-smokers compared with never-smokers, although this did not quite reach conventional levels of statistical significance (p = 0.059). Neither did the association differ between those with and without bronchitis (p = 0.53) or between those with and without emphysema (p = 0.91).

It is possible that people with lower lung function could spend less time exercising outdoors, and this could lead to lower concentrations of serum vitamin
D in these individuals. Alternatively, vitamin D status could be related to other nutritional covariates that reflect general health status, such as taking vitamin D supplements or drinking more milk. It could also conceivably be linked to a greater intake of antioxidants such as vitamin C, vitamin E, beta-carotene, or selenium, which have previously been shown to be related to lung function. For this reason, we also examined the relationship among 25-hydroxyvitamin D level, FEV1, and FVC following adjustment for leisure time physical activity, intake of vitamin D supplements, frequency of milk intake, and level of serum antioxidants, in addition to all the other variables listed in Table 1. Table 4 shows that vigorous physical activity was associated with a higher FEV1 and FVC, with a difference in FEV1 of 146 mL between those undertaking vigorous physical activity and those who were inactive. Despite this, there was still a significant association between 25-hydroxyvitamin D level and lung function after adjusting for leisure time activity and nutritional covariates. The adjusted mean difference between the highest and lowest quintile for 25-hydroxyvitamin D in this analysis was 106 mL (SE, 24 mL) for FEV1 and 142 mL (SE, 29 mL) for FVC.

**Discussion**

We have found a dose-response relationship between the serum concentration of 25-hydroxyvitamin D and FEV1. Even after adjustment for age, gender, ethnicity, height, and smoking, all of which can affect lung function, and for BMI, which can affect both lung function and vitamin D concentrations, the mean difference between the lowest quintile of 25-hydroxyvitamin D and the next quintile was 79 mL. This increased to 126 mL when the lowest and highest quintiles were compared. The difference in FEV1 between the highest and lowest quintiles of vitamin D is substantial, and is greater than the difference in FEV1 between individuals who had never smoked and ex-smokers, which was 83 mL.

There was no difference in the FEV1/FVC ratio between the highest and lowest quintiles of vitamin D, and this suggests that in the study population as a whole...
the reduction in FEV₁ and FVC in the lowest quintile of vitamin D is not attributable to the development of airflow obstruction. While the difference in FEV₁ between the highest and lowest quintiles of 25-hydroxyvitamin D was greater in those with a diagnosis of chronic bronchitis (248 mL) or emphysema (344 mL) than for the other participants, a test for an interaction between these diagnoses and the serum 25-hydroxyvitamin D level was not significant.

Although there is a relationship between vitamin D level and lung function, this does not establish the relationship as causal. One potential confounding factor is physical activity. One could argue that individuals with poor lung function may be exposed to less sunlight because they are less likely to go outside and exercise because of shortness of breath, but this does not appear to explain our findings. One could argue that the individuals who were the least likely to exercise because they were short of breath would be those with a diagnosis of asthma, chronic bronchitis, or emphysema. When they were excluded from the analysis, there was no effect on the relationship between vitamin D level and lung function. FEV₁ peaks between 18 and 25 years of life, and then plateaus before declining with age. Although the lungs do not grow in size after early adult life, it is likely that tissue remodeling and repair occur in the lungs throughout life. Although the number of elastic fibers in the alveolar walls decrease with age, there is at the same time an increase in type III collagen levels. There are a number of ways in which vitamin D may influence the remodeling of tissue, including the inhibition of matrix metalloproteinases, which are involved in the digestion of extracellular matrix as well as effects on the proliferation of fibroblasts and on the synthesis of collagen.

A previous analysis of the NHANES III data found a relationship between serum concentrations of antioxidant nutrients and lung function. A 1-SD increase in levels of serum vitamin C, vitamin E, beta-carotene, and selenium was associated with increases in FEV₁ of 28.1, 49.1, 27.5, and 23.7 mL, respectively. One could argue that confounding could have arisen because individuals with high serum concentrations of 25-hydroxyvitamin D may also have had higher concentrations of these antioxidants. It is also possible that 25-hydroxyvitamin D concentrations could have been influenced by the intake of milk or vitamin supplements, containing vitamin D, and this might happen more often in individuals who were in better health. However, following adjustment for leisure time activity, antioxidants and the intake of milk and supplements containing vitamin D, the strength of the associations among 25-hydroxyvitamin D, FEV₁, and FVC was only slightly reduced, with differences in FEV₁ and FVC between the highest and lowest quintiles of 25-hydroxyvitamin D of 106 and 142 mL, respectively. Nonetheless, we cannot exclude the possibility that our findings are due to confounding that we have not been able to identify.

One can speculate as to why higher concentrations of vitamin D are associated with better lung function. FEV₁ peaks between 18 and 25 years of life, and then plateaus before declining with age. Although the lungs do not grow in size after early adult life, it is likely that tissue remodeling and repair occur in the lungs throughout life. Although the number of elastic fibers in the alveolar walls decrease with age, there is at the same time an increase in type III collagen levels. There are a number of ways in which vitamin D may influence the remodeling of tissue, including the inhibition of matrix metalloproteinases, which are involved in the digestion of extracellular matrix as well as effects on the proliferation of fibroblasts and on the synthesis of collagen.

One way to establish whether there is a causal relationship between concentrations of vitamin D and lung function would be an intervention study in individuals with low serum concentrations of vitamin D.
D. It would be of interest to see whether supplementation with vitamin D reduced the decline in lung function over time, although this would necessarily be a large study and would involve follow-up over several years.

References