Low 25-hydroxyvitamin D levels are associated with decreased vital capacity of lung.

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<ABSTRACT>

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Background : Many studies suggest a role for vitamin D in respiratory diseases, but the effect of vitamin D on pulmonary function has not been studied extensively.

Objective : We investigated whether serum vitamin D concentration might be associated with lung function.

Methods : This study was based on the data acquired in the second year (2008) of the fourth National Health and Nutrition Examination Survey, a cross-sectional survey that was conducted from 2007 to 2009. The analysis included 2205 subjects who were older than 40 years and had complete data from both pulmonary function tests and serum 25-hydroxyvitamin D (25(OH)D) concentrations. Participants were divided into quartile categories of serum 25(OH)D concentration.

Results : Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were positively associated with increasing serum concentrations of 25(OH)D after adjustment with age, gender, smoking status, cigarette pack-years smoked, height, body weight, daily energy intake, intake of vitamin supplements, regions, occupations and physical activity. However, the FEV_1/FVC ratio was not significantly associated with serum 25(OH)D levels.

Conclusions : The results suggest that low vitamin D level are associated with deficits in lung function by not airway obstruction but decreased vital capacity.

Key words : vitamin D, lung function, vital capacity

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I. INTRODUCTION

It has long been known that vitamin D plays an important role in bone and mineral metabolism. Most of vitamin D is obtained by synthesis in the skin during exposure to sunlight and some is obtained either from the diet or from vitamin D supplements. Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D (25(OH)D), which is the major circulating form of vitamin D and is measured clinically to determine a subject's vitamin D status. 25(OH)D is metabolized in the kidneys to its active form, 1,25-dihydroxyvitamin D.[1,2] Vitamin D deficiency is closely associated with the occurrence of metabolic bone diseases such as rickets, osteomalacia and osteoporosis.[1,3] Recently, the discovery that most cells and tissues in the body have a vitamin D receptor and that some of them have the enzyme that converts the primary circulating form of vitamin D to the active form has provided new insights into the action of this vitamin. This has attracted increasing attention from medical researchers.

Vitamin D has nonskeletal functions including the regulation of cell proliferation, differentiation and immune function and is potentially involved in the development of many diseases.[2] Low vitamin D levels are associated with chronic illnesses, including autoimmune disease, infectious diseases and common cancer.[2,4] The vitamin D axis has also been implicated in the pathogenesis of respiratory disease. In a cross-sectional study based on the United States Third National Health and Nutrition Examination Survey (NHANES III), strong positive associations between serum vitamin D levels and lung function were reported.[5] A recent study observed that vitamin D deficiency occurs frequently in patients with chronic obstructive pulmonary disease (COPD) and that the level of deficiency was correlated with the severity of COPD.[6] On the other hand, in another population-based cross-sectional study, there was no positive association between serum concentrations of 25(OH)D and lung function after controlling for confounding factors.[7] That study found weak evidence to suggest that individuals with higher serum concentrations of 25(OH)D were more likely to have airflow obstruction. In one study that examined longitudinal data of lung function in continuous smokers, there was no difference in baseline 25(OH)D concentrations between individuals who had a rapid decline in lung function and those with a slow decline.[8] As mentioned above, studies that evaluated the association between serum vitamin D level and lung function measures have reported conflicting results[5–10] and the effect of 25(OH)D on pulmonary function has not been studied extensively.

Therefore, the aim of the present study was to investigate whether vitamin D status might correlate with lung function in the Korean population based on the Fourth Korean National Health and Nutrition Examination Survey (KNHANES IV).

II. MATERIALS AND METHODS

1. Study participants

KNHANES IV was carried out from 2007 to 2009 by the Division of Chronic Disease Surveillance, Korea Centers for Disease Control and Prevention. This study is based on the data acquired in the second year (2008) of KNHANES IV. The survey comprised a health interview, and an evaluation of nutrition and health. After an initial interview at home, participants visited mobile centers where they underwent an extensive physical examination, pulmonary function testing and blood sampling. The study methods have been published in more detail elsewhere.[11]

A total of 7108 adults who were ≥ 20 years of age participated in the survey in 2008. Of these, 3418 individuals underwent spirometry and 5921 had serum 25(OH)D levels measured. We analyzed 2205 subjects who were older than 40 years and obtained both appropriate pulmonary function test results and serum 25(OH)D concentrations. Information was collected at the home interview on variables including age, gender, current smoking status, daily food intake, the frequency of intake of vitamin or mineral supplements and the frequency of undertaking a range of common physical activities. Information on the intake of vitamin or mineral supplements in the past year was collected by a question asking, “Have you taken any vitamin or minerals over 2 weeks in the past year?”

Regions in the survey were categorized into 16 administrative districts: urban or rural. Occupation of the subjects was classified into three groups according to the likely daily duration of exposure to sunlight. Group A (agriculture, forestry and fishery) comprised outdoor occupations. Group B subjects underwent manual labor, engineering, assembling and technical work. Group C comprised managers, specialists, clerical workers, salespersons, service personnel, housewives and students. Regular exercise was indicated as ‘yes’ when the subject performed moderate or severe exercise on a regular basis, regardless of whether this was indoor or outdoor exercise. This needed to be for more than 30 min at a time and more than five times per week in the case of moderate exercise such as slow swimming, playing tennis doubles, volleyball, badminton, table tennis or carrying light objects for more than 20 min at a time. Severe exercise was classed as exercising at least three times a week in activities such as running, climbing, fast cycling, fast swimming, playing football, basketball, jumping rope, squash or singles tennis, or carrying heavy objects. Regular walking activity was recorded as ‘yes’ when the subject walked for more than 30 min at a time and more than five times per week, regardless of whether this was indoors or outdoors.[11] All the participants in this survey signed an informed consent form and the study was approved by the institutional review boards of the Yonsei University Severance Hospital.

2. Pulmonary function

All pulmonary function measurements were performed with standardized equipment according to American Thoracic Society/European Respiratory Society guidelines. Spirometric values were prebronchodilator measurements and absolute values were expressed as percentage predicted of reference values.

3. Measurement of serum 25-hydroxy vitamin D

Because the serum level of 25(OH)D is considered the best circulating biomarker of vitamin D metabolic status, it was measured using a radioimmunoassay (DiaSorin, Stillwater, MN, USA) and a gamma counter (1470 Wizard, Perkin-Elmer Finland). The interassay coefficients of variation were 11.7%, 10.5%, 8.6% and 12.5% at 8.6, 22.7, 33.0 and 49.0 ng/ml, respectively.

4. Statistical analyses

Statistical analyses were performed using SPSS® (Version 19.0, Chicago, IL, USA). A descriptive analysis of univariate factors was performed using quartiles of 25(OH)D concentrations among the survey subjects. *P* values were calculated by means of the Cochran–Armitage test for trend for binary predictors and by linear regression for continuous variables. Univariate and multiple linear regressions were used to analyze the association between serum 25(OH)D concentrations and lung functions.

III. RESULTS

1. Characteristics of the study population

The analysis included 2205 subjects who were older than 40 years and had complete data from both pulmonary function tests and serum 25(OH)D measures. The baseline characteristics of the study participants are given in Table 1. Their mean age was 56 years and 933 were male (42.3%). Forty percent of participants were current or past smokers and 392 (20.3%) individuals reported taking vitamin supplements. The mean 25(OH)D level was 20.7 ± 7.7 ng/mL (range 3.1–50.8). Participants were also divided into quartile (Q) categories of serum 25(OH)D concentrations: Q1 <15.0 ng/mL; Q2 $15.0 \leq 20.2$ ng/mL; Q3 $20.2 \leq 26.3$ ng/mL) and Q4 ≥ 26.3 ng/mL. The serum 25(OH)D concentration was higher in men than in women and higher in older populations than younger. There were statistically significant trends toward a higher proportion of smokers, greater body height and weight with increasing quartiles of 25(OH)D. Whereas a higher daily energy intake was associated with a higher level of 25(OH)D, the intake of vitamin supplements was not. Subjects who usually worked indoors and lived in urban areas were associated with lower levels of 25(OH)D.

Table 1. Characteristics of participants according to serum 25-hydroxyvitamin D concentrations

	Total	Quartile of serum 25(OH)D* concentration				*P*-value for trend
		Q1	Q2	Q3	Q4	
Age (years)	56.5 ± 11.0	56.1 ± 11.8	55.2 ±10.4	56.4 ± 10.9	58.2 ± 10.6	<0.001
Gender						<0.001
Male	933 (42%)	132 (24%)	202 (37%)	287 (52%)	312 (57%)	
Female	1272 (58%)	419 (76%)	350 (64%)	264 948%)	239 (43%)	
Height (cm)	160.1 ± 8.7	158.0 ± 7.7	159.5 ± 8.7	161.5 ± 8.8	161.2 ± 8.9	<0.001
Body weight (kg)	62.1 ± 10.1	60.4 ± 9.9	62.6 ± 10.1	63.4 ± 10.0	62.2 ± 10.1	0.001
BMI+ (kg/m^2)	24.2 ± 2.9	24.2 ± 3.2	24.4 ± 2.9	24.2 ± 2.6	23.9 ± 2.9	0.074
Smoking status						<0.001
Never	1331 (60%)	393 (71%)	370 (67%)	293 (53%)	275 (50%)	
Ex or Current	872 (40%)	158 (29%)	180 (33%)	258 (47%)	276 (50%)	<0.001
Pack-years	5.7 ± 14.1	2.3 ± 7.4	4.0 ±11.4	8.4 ±17.7	8.5 ±14.1	<0.001
Daily energy intake (kcal)	1800 ± 714	1646 ± 645	1778 ± 740	1860 ± 699	1917 ± 740	<0.001
Intake of vitamin supplements	392 (20%)	96 (20%)	103 (22%)	91 (19%)	102 (21%)	0.981
Regions						<0.001
Rural area	890 (40%)	156 (28%)	212 (38%)	223 (40%)	299 (54%)	
Urban area	1315 (60%)	395 (72%)	339 (62%)	328 (60%)	253 (46%)	
Occupation						<0.001
A	336 (15%)	25 (5%)	64 (12%)	86 (16%)	161 (29%)	
B	457 (21%)	95 (17%)	122 (22%)	116 (21%)	124 (23%)	
C	1407 (64%)	429 (78%)	363 (66%)	349 (63%)	266 (48%)	
Physical activity						<0.001
Regular exercise, Yes	620	106	144	170	200	
Regular walk, Yes	635	166	149	161	159	

25(OH)D* : 25-hydroxyvitamin D

BMI+ : Body mass index

2. Lung function by quartile of serum 25(OH)D concentrations

Table 2 shows the mean lung function measures by quartile of serum 25(OH)D concentrations. The mean forced expiratory volume in 1 s (FEV_1) values in the lowest and highest quartiles of 25(OH)D levels were 2.44 L and 2.67 L, respectively. The mean forced vital capacity (FVC) values in the lowest and highest quartiles of 25(OH)D levels were 3.13 L and 3.52 L, respectively. FEV_1 and FVC tended to increase with increasing serum concentrations of 25(OH)D, but the FEV_1/FVC ratio tended to decrease.

Table 2. Mean lung function by quartile of serum 25(OH)D concentrations

	Total	Quartile of serum 25(OH)D concentration				*P*-value for trend
		Q1	Q2	Q3	Q4	
FEV_1/FVC %, predicted	0.77 ± 0.08	0.78 ± 0.07	0.78 ± 0.07	0.77 ± 0.07	0.76 ± 0.08	<0.001
FEV_1, L	2.60 ± 0.69	2.44 ± 0.61	2.58 ± 0.68	2.70 ± 0.72	2.67 ± 0.71	<0.001
FEV_1 %, predicted	91.0 ± 14.0	90.5 ± 14.2	90.6 ± 13.9	91.5 ± 15.1	91.6 ± 15.6	0.145
FVC, L	3.37 ± 0.85	3.13 ± 0.74	3.31 ± 0.86	3.51 ± 0.88	3.52 ± 0.85	<0.001
FVC %, predicted	91.9 ± 12.9	91.3 ± 12.9	91.4 ± 12.8	92.1 ± 12.9	92.8 ± 12.8	0.040

Table 3 shows the associations between lung function and serum 25(OH)D concentrations after adjustment for age, gender, cigarette pack-years smoked, height, daily energy intake and occupations.

Serum 25(OH)D concentrations were shown to be positively associated with FEV_1 and FVC by univariate linear regressions and this association remained significant for levels of more than 20 ng/mL. The differences in FEV_1 and FVC values between the lowest and highest quartiles of 25(OH)D levels were 0.066 L (95% CI 0.04-0.12, p-value =0.021) and 0.074 L (95% CI 0.01-0.14, p-value =0.024), respectively. However, the FEV_1/FVC ratio was not significantly associated with serum concentrations of 25(OH)D by multiple linear regression analysis except for subjects in Q3.

Table 3. Relationship between serum 25(OH)D concentrations and FEV_1, FVC and FEV_1/FVC

	FEV_1					
	Unadjusted			Mutivariate Model		
Quartile of 25(OH)D	**Beta Coefficient***	**95% CI**	***P*-value**	**Beta Coefficient***	**95% CI**	***P*-value**
Q1	-			-		-
Q2	0.142	0.062 to 0.223	0.001	0.012	-0.041 to 0.064	0.662
Q3	0.272	0.191 to 0.352	<0.001	0.095	0.041 to 0.149	0.001
Q4	0.237	0.156 to 0.317	<0.001	0.066	0.039 to 0.122	0.021

	FVC					
	Unadjusted			Mutivariate Model		
Quartile of 25(OH)D	**Beta Coefficient***	**95% CI**	***P*-value**	**Beta Coefficient***	**95% CI**	***P*-value**
Q1	-			-		-
Q2	0.179	0.081 to 0.277	<0.001	0.010	-0.049 to 0.070	0.733
Q3	0.383	0.285 to 0.482	<0.001	0.081	0.019 to 0.143	0.010
Q4	0.389	0.290 to 0.487	<0.001	0.074	0.010 to 0.138	0.024

	FEV_1/FVC					
	Unadjusted			Mutivariate Model		
Quartile of 25(OH)D	**Beta Coefficient***	**95% CI**	***P*-value**	**Beta Coefficient***	**95% CI**	***P*-value**
Q1	-			-		-
Q2	0.002	-0.007 to 0.011	0.640	0.002	-0.006 to 0.011	0.609
Q3	-0.007	-0.016 to 0.002	0.134	0.010	0.002 to 0.019	0.021
Q4	-0.019	-0.028 to -0.010	<0.001	0.003	-0.006 to 0.012	0.542

*Adjusted for age, gender, height, pack years, daily energy intake and occupations

IV. DISCUSSION

In this population-based cross-sectional study, after adjustment for potential confounders, we found that there was a significant association between serum concentrations of 25(OH)D and FEV_1 and FVC, but no difference in the FEV_1/FVC ratio. This finding suggests that reductions of FEV_1 and FVC are not attributable to the development of airflow obstruction.

The best evidence to date regarding a relationship between 25(OH)D levels and lung function is the United States NHANES III.[5] This was an observational, cross-sectional survey that analyzed data collected from more than 14,000 adults older than 20 years of age. There was a dose-dependent association between a lower serum 25(OH)D level and reduced pulmonary function, as assessed by FEV_1 and FVC. Adjusting for confounders (such as age, gender, smoking history, height and physical activity) demonstrated a mean difference of FEV_1 by 106 mL and FVC by 142 mL between the lowest and highest quintiles of vitamin D levels. However, there was no difference in the FEV_1/FVC ratio between the highest and lowest quintiles of 25(OH)D levels. Our findings are consistent with the results of that study. These two large population-based cross-sectional studies have shown that lower concentrations of 25(OH)D might be associated with decreased lung function caused not by airway obstruction but by decreased vital capacity.

Although many studies suggest that 25(OH)D deficiency is associated with reduced lung function, data confirming a causal relationship between 25(OH)D levels and lung function have been lacking. A recent study offered the first concrete evidence linking 25(OH)D deficiency with deficits in lung function and altered lung structure.[12] It demonstrated a direct role for 25(OH)D in causing decreased lung function in the absence of known confounders such as physical inactivity, confirming the assertion by epidemiological studies that there is a relationship between 25(OH)D deficiency and lung function. The results show that 25(OH)D deficiency causes deficits in lung function, which are primarily explained by differences in lung volume. NHANES III and our present study support these results and explanations.

Although there is evidence for a direct role for 25(OH)D in causing decreased lung function, the mechanisms are unclear. Proposed mechanisms are that 25(OH)D could influence lung function by influencing the remodeling of tissue via matrix metalloproteinases (MMPs) and the synthesis of collagen.[13] Tissue MMPs and their inhibitors control remodeling in tissues. Some studies reported that vitamin D regulates extracellular matrix homeostasis in tissues, within particular lung and skin tissue via the control of MMPs and transforming growth factor-β.[14] Timms et al. examined the hypothesis that 25(OH)D status modulates the MMP system in a population with a high prevalence of 25(OH)D deficiency.[15] They showed that deficiency was associated with increased circulating MMP9, correctable by supplementation. These findings help provide a possible mechanism to support the connection between 25(OH)D deficiency and lung inflammation/degradation.

Clinical studies have indicated that 25(OH)D status is positively associated with muscle strength and physical performance and inversely associated with risk of falling.[16,17] Vitamin D supplementation has shown to improve tests of muscle function and reduce the incidence of falls.[18] Therefore we speculate that low levels of 25(OH)D cause muscle weakness and consequently influence the vital capacity of the lungs.

V. CONCLUSION

The results of this study suggest that low 25-hydroxyvitamin D levels are associated with deficits in lung function by decreased vital capacity.

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< ABSTRACT(IN KOREAN)>

낮은 혈청 vitamin D는 감소된 폐활량과 관계가 있다.

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김 서 윤

많은 연구에서 호흡기 질환에서 vitamin D가 관여한다고 보고하고 있지만 폐기능에 대한 vitamin D 효과가 광범위하게 연구되지는 않았다.

이 연구의 목적은 혈청 vitamin D 농도와 폐기능과의 관련성이 있는 지 알아보는 것이다.

2007년부터 2009년까지 수행된 단면 조사인 제 4기 국민건강영양조사 (2008년)의 자료를 바탕으로 본 연구를 수행하였다. 40세 이상의 성인 중 적절하게 폐기능을 수행하고 혈청 vitamin D 농도를 측정한 2205명을 대상으로 분석하였으며 vitamin D 농도를 사분위수로 나누어 살펴보았다.

연령, 성별, 키, 흡연량, 일일 에너지 섭취량 그리고 직업을 보정한 후 forced expiratory volume in 1 second (FEV_1)과 forced vital capacity (FVC)는 혈청 vitamin D 농도가 증가함에 따라 증가하는 양의 관계를 보였으나 FEV_1/FVC는 혈청 vitamin D 농도와 관련이 없었다.

이 결과를 바탕으로 낮은 혈청 vitamin D 농도는 기도 폐쇄가 아니라 폐활량 감소와 관련하여 폐기능 감소를 유발한다고 추정할 수 있겠다.

핵심되는 말 : vitamin D, 폐기능, 폐활량