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Association of serum 25-hydroxy-vitamin D with lung function and fractional exhaled nitric oxide.

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Abstract

Vitamin D plays a major role in various physiological functions and body homeostasis. The aim of this study was to examine the relationship between serum 25-hydroxyvitamin D status with lung functions and Fractional Exhaled Nitric Oxide (FeNO). 113 (55 males and 58 females) apparently healthy participants were recruited. Participants were divided into two main groups based on their gender and vitamin D levels. Group 1 included male participants categorized according to deficient vitamin D level <30 ng/ml (n=35) and sufficient vitamin D level 30-80 ng/ml (n=20). The second group included 58 female participants with deficient vitamin D level <30 ng/ml (n=19) and sufficient vitamin D level 30-80 ng/ml (n=39). Vitamin D was measured by chemiluminescence immunoassays technique, lung Function parameters were recorded by using an electronic spirometer and Fractional Exhaled Nitric Oxide (FeNO) was measured by using Niox Mino. No association of vitamin D levels was found with reduced lung functions and FeNO levels.

Keywords: Vitamin D, Lung functions, Fractional exhaled nitric oxide.

Abbreviations

Forced Vital Capacity (FVC), Forced Expiratory Volume in first second (FEV1), Forced Expiratory Ratio (FEV1/FVC%), Peak Expiratory Flow (PEF), Forced Expiratory Flow 25% (FEF-2 5%), Forced Expiratory Flow 50% (FEF-50%), Forced Expiratory Flow 75% (FEF-75%), Fractional Exhaled Nitric Oxide (FeNO), Vitamin D Binding Protein (DBP).

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Introduction

Vitamin D is a steroid vitamin that plays a major role in various physiological functions and body homeostasis. It has an immune-modulatory and anti-inflammatory effect [1]. The prevalence of vitamin D deficiency is increasing globally even in the countries near the equator where sun exposure is high [2]. Vitamin D deficiency has been recognized as a major public health problem worldwide [3]. Vitamin D deficiency is becoming an endemic in many parts of the world and its deficiency can cause various health problems and poses a great threat to human health. Vitamin D deficiency has been associated with various autoimmune, inflammatory disorders and malignancy [4] and has also been linked to respiratory illness including asthma and chronic obstructive pulmonary disease. Recent reports suggest that vitamin D deficiency is associated with impaired ventilatory functions [4,5]. However, there is a dearth of research reports confirming a relationship between vitamin D and lung function.

Spirometry and Fractional Exhaled Nitric Oxide (FeNO) are mainly important in various clinical and occupational settings [6,7]. Lung functions in addition to Fractional Exhaled Nitric Oxide in subjects with an association of Vitamin D have not been collectively and extensively studied. Therefore, the aim of this study was to investigate the association of serum 25-hydroxy vitamin D with lung function and Fractional Exhaled Nitric Oxide.

Subjects and Methods

Subject selection

This cross sectional study was conducted in the Department of Physiology, College of Medicine, King Saud University, Riyadh, Saudi Arabia. For this study, 113 (55 males and 58 females) apparently healthy participants, with mean age range 18-60 years were recruited. Participants were divided into two main groups based on their gender and vitamin D levels. Group 1 included 55 male participants categorized according to vitamin D levels, namely; deficient vitamin D level <30 ng/ml (n=35) and sufficient vitamin D level 30-80 ng/ml (n=20). Group 2 included 58 female participants categorized according to vitamin D levels, namely deficient vitamin D level <30 ng/ml (n=19) and sufficient vitamin D level 30-80 ng/ml

(n=39). All the subjects were matched for age, weight, height, ethnicity and socioeconomic and demographic status. A comprehensive clinical history of each subject was takes to decide whether to include in the research or not.

Exclusion criteria

Subjects with identified cases of anaemia, blood diseases, diabetes mellitus, bronchial asthma, malignancy and drug addicts were excluded from the study. Subjects who smoked cigarette or shisha were also excluded from the study [7,8]. We also excluded the subjects whose serum vitamin D was more than >80 ng/mL to minimize the vitamin D toxicity effect.

Potential confounders

The potential confounding factors were carefully considered due to their known or plausible associations with impact and outcomes. These factors include age, gender, ethnicity, height, weight, health status, socioeconomic position and outdoor activity.

Measurement of 25 (OH) vitamin D

For the determination of serum 25 (OH) vitamin D concentrations, about 5-6 ml of blood was obtained from each participant by vein puncture method. Serum 25 (OH) vitamin D levels were measured in nmol/L by using direct chemiluminescence immunoassays (LIASON-Diasorin) [9]. It is commonly used for the determination of 25 (OH) vitamin D in serum or plasma [10]. It has an excellent detection range [11], and is a valid tool for the determination of serum 25 (OH) vitamin D concentrations [12].

Spirometry

The ventilator lung function parameters were measured by using an electronic spirometer SPIROVIT SP-1 (Schiller, Switzerland). Lung function test parameters were recorded including Forced Vital Capacity (FVC), Forced Expiratory Volume in first second (FEV1), Forced Expiratory Ratio (FEV1/FVC%), Peak Expiratory Flow (PEF), Forced Expiratory Flow 25% (FEF-25%), Forced Expiratory Flow 50% (FEF-50%) and Forced Expiratory Flow 75% (FEF-75%). The established techniques in performing the various lung function tests for this study were based on American Thoracic Society of Standardization [13].

Fractional Exhaled Nitric Oxide

The Fractional Exhaled Nitric Oxide [FeNO] was determined by using a Niox Mino, Aerocrine, Solna and Sweden. The FeNO device was pre-calibrated and programed for 300 measurements. Tests were recorded at a fixed time of the day to minimize the diurnal variation. The established procedures in performing FeNO test was based on the American Thoracic Society/ERS Standardization procedures [14]. The design and execution of this study was approved by the Institutional Review Board, Department of Family and Community Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia and informed consent was obtained from all the study participants.

Statistical analysis

The data were entered into the computer and analysed by using the Statistical Package for Social Sciences [SPSS for Windows, version 21.0]. Unpaired student's t-test (parametric test) was applied to test the difference in the means between the variables. The level of significance was considered at $p<0.05$.

Results

Table 1 summarizes the comparison of the anthropometric variables between the sufficient and deficient groups. The mean age of male sufficient group was 30.00 ± 12.18 years (mean ± SD), height 172.70 ± 9.91 cm (mean ± SD), weight 77.70 ± 18.34 kg (mean ± SD). The mean age of the deficient male group was 25.34 ± 6.70 years (mean ± SD), height 173.03 ± 6.15 cm (mean ± SD), weight 79.46 ± 21.35 kg (mean ± SD). However, the mean age of female sufficient group was 27.26 ± 8.54 years (mean ± SD), height 162.41 ± 7.19 cm (mean ± SD), weight 67.62 ± 20.87 kg (mean ± SD). The mean age of the deficient female group was 23.05 ± 3.44 years (mean ± SD), height 161.21 ± 6.04 cm (mean ± SD), weight 65.26 ± 17.07 kg (mean ± SD). There was a no significant difference in the age, weight and height of the subjects between the groups.

Table 1. *Comparison of anthropometric, lung function and FeNO between the male subjects with sufficient and deficient vitamin D levels.*

Male Group (n=55)			
Parameters	Vitamin D <30 (n=35)	Vitamin D 30-80 (n=20)	P-value
Age (years)	25.34 ± 6.70	30.00 ± 12.18	0.072
Height (cm)	173.03 ± 6.15	172.70 ± 8.91	0.872
Weight (kg)	79.46 ± 21.35	77.70 ± 18.34	0.759
FVC (lit)	5.26 ± 1.13	4.79 ± 0.81	0.108
FEV1 (lit/sec)	4.14 ± 0.09	4.00 ± 0.08	0.574
FEV1/FVC (Ratio)	79.55 ± 11.95	82.94 ± 11.99	0.317
PEF (lit/sec)	6.56 ± 2.35	6.65 ± 2.40	0.889
FEF 25% (lit/sec)	6.11 ± 2.21	6.43 ± 2.51	0.628
FEF 50% (lit/sec)	4.77 ± 1.59	5.02 ± 1.78	0.599
FEF 75% (lit/sec)	2.49 ± 1.14	2.74 ± 1.16	0.445
FeNO ppb	29.34 ± 21.26	24.75 ± 10.96	0.373
Vitamin D ng/ml	19.82 ± 6.76	46.79 ± 15.94	0.0001

Note: Values are presented in Mean ± Std. Deviation

Table 1 also demonstrates the comparison of the lung function parameters and Fractional Exhaled Nitric Oxide between the male group with sufficient and deficient vitamin D levels. The lung function parameters of deficient versus sufficient male

group were as follows: FVC 4.79 ± 0.81 *vs.* 5.26 ± 1.13 (p=0.108); FEV1 4.00 ± 0.08 *vs.* 4.14 ± 0.09 (p=0.57); FEV1/FVC Ratio 82.94 ± 11.99 *vs.* 79.55 ± 11.95 (p= 0.317); PEF 6.65 ± 2.40 *vs.* 6.56 ± 2.35 (p=0.889); FEF-25% 6.43 ± 2.51 *vs.* 6.11 ± 2.21 (p=0.62), FEF-50% 5.02 ± 1.78 *vs.* 4.77 ± 1.59 (p=0.599); FEF-75% 2.74 ± 1.16 *vs.* 2.49 ± 1.14 (p=0.44).

Table 1 also summarize the comparison of the Fractional Exhaled Nitric Oxide between the male subjects with sufficient and deficient vitamin D status. There was no significant difference in FeNO in male subjects with deficient versus sufficient groups, 24.75 ± 10.96 *vs.* 29.34 ± 21.26 (p=0.37) (Table 1) and in female subjects 18.79 ± 18.43 *vs.* 20.53 ± 22.32 (p=0.775) (Table 2).

Table 2. *Comparison of anthropometric, lung function and FeNO between the female subjects with sufficient and deficient levels of vitamin D.*

Female Group (n=58)			
Parameters	Vitamin D <30 (n=19)	Vitamin D 30-80 ng /ml (n=39)	P value
Age (years)	23.05 ± 3.440	27.26 ± 8.543	0.044
Height (cm)	161.21 ± 6.04	162.41 ± 7.19	0.534
Weight (kg)	65.26 ± 17.07	67.62 ± 20.875	0.672
FVC (lit)	3.82 ± 0.59	3.65 ± 0.69	0.368
FEV1 (lit/sec)	3.22 ± 0.48	2.98 ± 0.49	0.091
FEV1/FVC (Ratio)	84.75 ± 9.66	83.09 ± 13.31	0.629
PEF (lit/sec)	5.811 ± 1.56	5.056 ± 1.56	0.089
FEF25% (lit/sec)	5.573 ± 1.47	4.841 ± 1.57	0.095
FEF50% (lit/sec)	4.159 ± 0.91	3.830 ± 1.24	0.308
FEF75% (lit/sec)	1.95 ± 1.00	2.12 ± 0.87	0.501
FeNO ppb	20.53 ± 22.32	18.79 ± 18.43	0.755
Vitamin D ng/ml	21.71 ± 4.24	49.12 ± 12.63	0.0001
Note: Values are presented in Mean ± Std. Deviation			

Table 3 summarizes the correlation between lung function parameters, Fractional Exhaled Nitric Oxide and vitamin D between the male and female subjects with sufficient and deficient vitamin D levels. There was a no significant difference in various parameters between the groups (Table 3).

Table 3. *Correlation between vitamin D and lung function parameters and FeNO.*

	Vitamin D <30 ng / ml		Vitamin D 30-80 ng /ml	
	Males (n=55)		Females (n=58)	
Parameters	Pearson Correlation	P value	Pearson Correlation	P- value
Age (years)	-0.199	0.150	0.169	0.202
Height (cm)	-0.096	0.488	0.105	0.430
Weight (kg)	-0.040	0.776	0.068	0.610
FVC (Lit)	0.099	0.477	-0.215	0.102
FEV1 (Lit/sec)	0.137	0.323	-0.125	0.346
FEV1/FVC Ratio	0.006	0.964	0.117	0.378
PEF (Lit/sec)	0.199	0.150	-0.005	0.971
FEF25% (Lit/sec)	0.188	0.173	-0.048	0.716
FEF50% (Lit/sec)	0.058	0.678	0.118	0.375
FEF75% (Lit/sec)	0.005	0.973	0.146	0.270
FeNO ppb	-0.077	0.578	0.067	0.614

Discussion

The prevalence of vitamin D deficiency is increasing globally and has been linked to various health problems. In the present study, we examined the relationship of serum 25-hydroxyvitamin D status with lung functions and Fractional Exhaled Nitric Oxide (FeNO) in Saudi adult community, but, we did not find any association of serum 25-hydroxy-vitamin D with impaired lung function and Fractional Exhaled Nitric Oxide. Previously, Thuesen et al. 2015 [15] reported that 25 (OH) vitamin D levels do not influence the development of asthma and allergy among adults. Moreover, their results did not support the notion that 25 (OH) vitamin D levels are associated with lung function impairment. Similarly, Berg et al. 2013 [16] conducted a study on the association of Vitamin D and vitamin D binding protein (DBP) with COPD and FEV1. They found that 25 (OH) vitamin D was not associated with DBP and DBP was not associated with FEV1.

Lange et al. 2012 [17] conducted a study to determine the effect of vitamin D deficiency and smoking on lung function. In the overall cohort, they found that, there was no significant effect of vitamin D deficiency on lung function or on lung function decline. Although, among smokers, vitamin D sufficiency appeared to have a protective effect on lung function and the rate of lung function decline, modifying the effect of smoking. Furthermore, Shaheen et al. 2011 [18] determined the possible role of serum 25 hydroxy vitamin D in respiratory disease and lung function. They found that total vitamin D intake was positively associated with forced expiratory volume in 1 s (FEV1). However, serum 25 (OH) vitamin D concentrations were not related to FEV1. Their findings did not confirm a positive association between serum 25 (OH) vitamin D concentrations and lung function. In the present study, we did not find an association between vitamin D concentration with pulmonary functions and FeNO. The present study findings are in consistent to the results from previous studies Thuesen et al. 2015 [15]; Berg et al. 2013 [16]; Lange et al. 2012 [17]; Shaheen et al. 2011 [18].

In contrast, Khan et al. [19] conducted a cross-sectional study and found a significant association between vitamin D levels and some pulmonary function variables FVC and FEV1, especially in overweight or obese men but they did not observe a notable influence of vitamin D deficiency on pulmonary

function among women. However, in the present study, we did not find any association between the lung function parameters and Vitamin D concentration. The most probable reason for this contradiction is that, in our study the entire sample size was well matched for age, gender, height, weight, ethnicity and socioeconomic status, however, Khan et al. [19] found the association mainly in the obese men and they did not observe any influence of vitamin D deficiency on pulmonary function in women. It is well established fact that obesity impairs the lung function Melo 2014 [20]; Davidson et al. 2014 [21]. We believe that, the lung function impairment might be the effect modifier of obesity rather than vitamin D levels. In another study, Semba et al. 2012 [22] reported that serum 25 (OH) vitamin D was associated with poor pulmonary function in older disabled women. The findings of the present study are in contradiction to Semba et al. 2012 [22]. As they have conducted the lung function in older and disabled women. The most probable reason for poor lung function is old age and disability. It is established fact that lung functions are decreased in old age and among disabled people [23]. Yao et al. 2014 [24] investigated the relationship of vitamin D status with lung function and FeNO in a children. They found a no significant association between serum 25 (OH) vitamin D levels and FeNO after adjusting for confounders. Similarly in the present study we did not find an association between vitamin D levels and FeNO.

Study strengths and limitations: This study has several strengths. Most notably, it was the first study to explore the relation between the lung functions, FeNO and vitamin D status. The analysis included age, height, weight, ethnicity and socioeconomically matched subjects. All of the Spiro metric, FeNO and Vitamin D measurements were carried at the fixed time of the day to minimize the diurnal variation.

One of the limitations of the present study is its cross-sectional nature that hampers to establish cause-and-effect relationships among pulmonary function, FeNO and vitamin D. The second limitation of the present study was a small sample size therefore; we suggest that in future large sample sized studies should be conducted to reach at the better conclusions. The third limitation of the current study was that the vitamin D concentration was measured only once for each participant. It is known that there is seasonal fluctuation in 25 (OH) vitamin D concentrations, with lower concentrations in the winter time because major percentage of vitamin D is acquired from exposure to sunlight [25]. Therefore, the measurement recorded was not a meaningful representation of the individual's average vitamin D concentration throughout the year. In addition, we did not know the (dietary and sunlight) habits of the participants over the previous 3-4 weeks before the collection of the blood for the measurement of vitamin D. As 25 (OH) vitamin D concentration depends on dietary intakes and exposure to sunlight [25].

Conclusion

The current investigation concluded that, vitamin D has no association with lung function impairments and FeNo levels. We suggest that large sample sized lung function studies along with FeNO measurements should be conducted to find association with vitamin D to get the better interpretation to establish the clinical relevance.

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