

THE ASSOCIATION OF SERUM 1, 25-DIHYDROXY VITAMIN D2 STATUS WITH ASTHMA IN A COMPARATIVE STUDY OF IRAQI ADULTS

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ABSTRACT : Vitamin D2 has an immunomodulatory effect on asthma. The association between vitamin D2 and asthma is still uncertain. The study aims to measure concentrations of vitamin D2 in the serum of asthmatic adults and to match these to asthma-free healthy controls. A cross-sectional comparative study had conducted from August 2020 to December 2020 in the adult respiratory clinic of the Merjan Teaching Hospital, Babylon, Iraq. The measurements of FeNo and vitamin D2 were obtained for asthmatic adults (n-127) and compared to (age and sex) matched, asthma-free a healthy control (n-113). Data had collected on planned performa and managed by SPSS-23. The authors used descriptive statistics for the features of the subjects. Fisher's-exact and Chi-squared test had applied for proportions. For the continuous variables, Students'-test and ANOVA had used to evaluate statistical significance depending on the distribution of the variable. Correlation of FeNo results with vitamin D2 had used. ROC analyses had been applied to estimate the predictability, sensitivity, specificity and significance of vitamin D2 for asthma diagnosis. The mean age of the studied participants was 34.1±6.9years, with no significant age differences between the groups. Serum vitamin D2 levels were ranged between 10.4-47.9ng/ml (19.7±6.9ng/ml). The serum vitamin D2 levels were parallel between the two groups, and only <10% show deficient levels (<20ng/ml). There was a positive non-significant correlation (r-0.067, p-0.54) of FeNo measures with serum levels of vitamin D2 among asthmatic patients. ROC curve analyses revealed that vitamin D2 showed less predictability and significance than FeNo to distinguish asthmatic from healthy subjects. In conclusion, the authors did not report any associations of serum vitamin D2 with the incidence of BAs, despite a significant difference in the distribution of vitamin D2 classes between the well-controlled and the poorly controlled asthma.

Key words : Asthma, FeNo, vitamin D2.

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INTRODUCTION

Bronchial asthma (BAs) is one of the common heterogeneous illnesses universally and has raised in incidence over the latest few decades. In Iraq, BAs constitute a major medical burden, both in adults and pediatric ages (Amjed, 2021; Qasim, 2020; Amjed H Abbas, 2021; Enas K Alkhazraji, 2021; Hayder Abdul-Amir Makki Al-Hindy, 2021). The etiology of BAs is multifaceted and possibly involves various associations of environmental and inherited factors (Al-Zayadneh *et al*, 2020). Lately, multiple clinical studies have recognized strong relations between vitamin D2 insufficiency and

high incidence of BAs, especially in patients with intractable forms. One explanation is vitamin D2 possesses an immunomodulatory and anti-inflammatory influence (Wang *et al*, 2019). Vitamin D2 has been known to increase pulmonary development in newborns during prenatal consumption, besides a prophylactic effect on wheeze, on later use though still controversial (Al-Zayadneh *et al*, 2020). Therefore, there has been massive awareness of the use of vitD in asthma (Ali and Nanji, 2017).

The widespread upswing in asthma necessitates new risk factors for asthma evolution, like vitamin D2

deficiency, which is vital to improve BAs control and help avoid the illness in early life (Al-Zayadneh *et al*, 2020).

Objective : The study aims to measure concentrations of vitamin D2 in the serum of asthmatic adults and to match these to asthma-free healthy controls.

MATERIALS AND METHODS

Study design and patients' collection

A cross-sectional comparative study had conducted from August 2020 to December 2020 in the adult respiratory clinic of the Merjan Teaching Hospital, Babylon, Iraq. Adults with physician-diagnosed BAs (n-127), aged 33.4±13.0 years, who were on regular follow-up in the hospital for at least the previous three months had registered into this study after exclusion of any chronic disease. Asthmatic patients were (age and sex) matched with healthy asthma-free controls (n-113).

Ethical consent

The initial protocol of the study had been agreed upon by the ethical committee of the health institutions, in addition to the accomplishment of informed written permission from each participant to be enrolled in the study.

Vitamin D2 and FeNo measurements

Venous samples (2.5cc) had collected and investigated on the same day for levels of vitamin D2, using Calbiotech® ELISA kit CA. Serum vitamin D2 level of more than 20 ng/ml was considered sufficient, a level between 12 and 20 ng/ml was insufficient, and a value less than 12 ng/ml was considered deficient, based on published rules and recommendations from preceding studies (Holick, 2011). FeNo results had registered from

patients' records. FeNo measures had evaluated according to the "guidelines of the American Thoracic Society".

Statistical analyses

Data had collected on planned performa and managed by SPSS-23. The authors used descriptive statistics to describe the features of the subjects. Fisher's-exact and Chi-squared test had applied for proportions. For the continuous variables, the Student's test and the ANOVA test had used to evaluate statistical significance, depending on the distribution of the variable. Correlation of FeNo results with vitamin D2 had used. ROC analyses had applied to estimate the predictability, sensitivity, specificity, and significance of vitamin D2 for asthma diagnosis.

RESULTS

Basic characteristics of the patients (n-127) and healthy groups (n-113) had shown in Table 1. The mean age of all participants was 34.1±6.9 years, with no significant differences in ages between the two groups. Asthmatic patients were heavier (p-0.04). A significant variation in the sex distribution had revealed between the studied groups (p-0.003). Less than half of asthma patients (41.7%) were on regular antiasthma therapy, for a mean duration of 8.024±3.9 years. Significant higher FeNo values among the patient group were observed compared to the controls (0.001). Serum vitamin D2 levels ranged between 10.4-47.9ng/ml (19.7±6.9ng/ml). The serum levels were parallel between the two groups. Around 2/3rd of all participants had normal vitamin D2 levels and only less than 10% show deficient levels (<20ng/ml).

Vitamin D2 levels were not differing significantly (p-

Table 1 : Basic characteristics of the patients' group (n-127) and healthy control (n-113).

	Total (n-240)	Asthma group (n-127)	Healthy group (n-113)	P-value
Age (years)	34.1±6.9	33.4±13.0	34.9±10.5	NS
BMI (kg/m ²)	29.9±5.4	30.7±5.6	28.8±5.0	0.04
Sex (no %)	Males (122)	55 (46.6)	67 (56.8)	0.003
	Females (118)	72 (61)	46 (39)	
Treatment history	On treatment	53 (41.7)		
	Without treatment	74 (58.3)		
Duration of asthma	8.024±3.9			
FeNo (ppb)	28.6±20.1	43.8±29.5	8.9±4.0	0.001
Vitamin D2 (ng/ml)	19.7±6.9	20.4±7.0	18.7±6.7	NS
Sufficient	147 (61.1%)	72 (56.9%)	75 (66.7%)	NS
Insufficient	71 (30%)	45 (35.3%)	26 (23.1%)	
Deficient	22 (8.9%)	10 (7.8%)	12 (10.3%)	

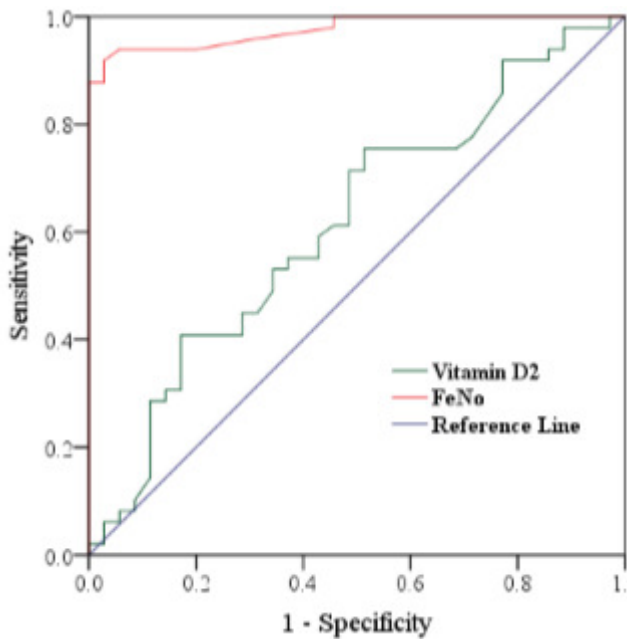


Fig. 1 : ROC curve for predictive features of vitamin D2 and FeNo for diagnoses of asthma.

0.34) in asthmatic patients between the treated and untreated groups (Table 2).

There was a positive non-significant correlation ($r=0.067$, $p=0.54$) of FeNo measures with serum level of Vitamin D2 among asthmatic patients (Table 3).

ROC-analysis inspected vitamin D2 and FeNo to examine their predictability for distinguishing asthma from healthy subjects (Fig. 1, Table 4). The FeNo reveals a high AUC, sensitivity, specificity, and significance at [95% CI 0.964-1.000]: 97.5%, 93.2%, 93.5% and $p=0.0001$, respectively. In comparison, vitamin D2 showed less predictability and significance: 61.2%, 68.3%, 54.8% and $p=0.085$ respectively at [95% CI 0.488-0.736] to distinguish asthmatic from healthy subjects.

Only a minority of the asthmatic patients (4.08%) exposed sufficient vitamin D2 serum levels (>29ng/ml), with a significant difference in the distribution of vitamin D2 classes between the well-controlled and the poorly controlled asthma (in terms of high measures of FeNo

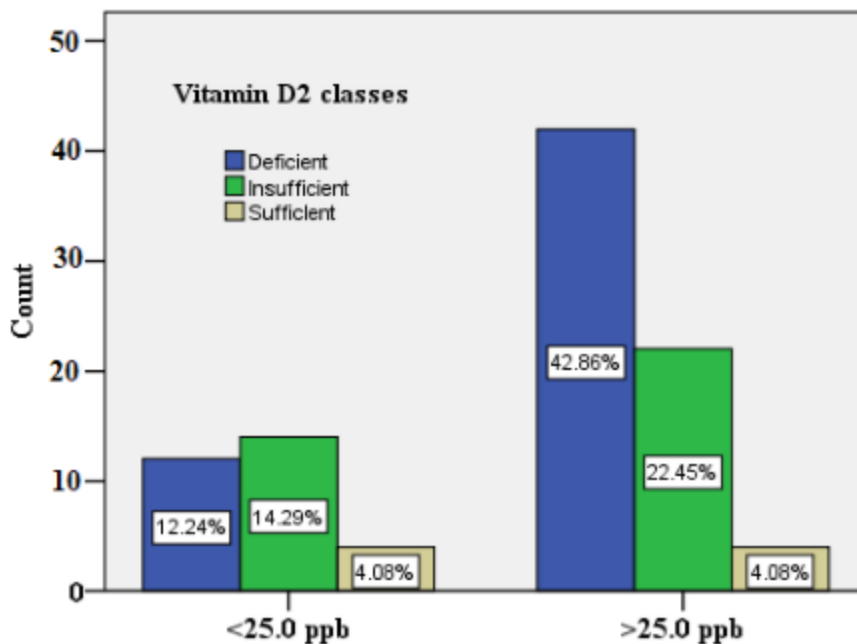


Fig. 2 : Distribution of classes of serum vitamin D2 according to the FeNo categories among asthmatic patients.

Table 2 : Difference in serum levels of vitamin D2 according to the history of treatment in asthmatic patients.

	Treatment	Mean± SD	P-value
Vitamin D2	on	21.9±10.9	0.341
	with out	20.2±5.1	

Table 3 : Correlation of FeNo results with vitamin D2 among asthmatic patients.

		Vitamin D2
FeNo	Correlation	0.067
	Significance	0.54

results).

DISCUSSION

In this paper, the discussion centers on the association of vitamin D2 status with asthma among Iraqi adults. The authors did not report any associations of serum vitamin D2 with the incidence of BAs. The serum vitamin D2 levels were parallel between the control and asthma groups and only <10% show deficient levels (<20ng/ml). Also, there was a nonsignificant association of vitamin D2 with a history of antiasthma treatment. On the other hand, a significant difference in the distribution of vitamin

Table 4 : ROC curve for predictive features of vitamin d2 and FeNo for diagnosis of asthma.

Variables	AUC	Significance	Specificity	Sensitivity	95% Confidence Interval	
Vitamin D2	0.612	0.085	68.3%	54.8%	0.488	0.736
FeNo	0.975	0.0001	93.2%	93.5%	0.946	1.000

D2 classes between the well-controlled and the poorly controlled asthma had been reported. Supporting our data are several studies that indicate that vitamin D2 levels do not influence the severity of BAs (Thuesen *et al*, 2015b; Liu *et al*, 2019; Agrawal, 2017; Gergen *et al*, 2013). In a recent Chinese meta-analysis assessing the association between asthma control and vitamin D2 status, non-significant differences had detected in ACT scores, FeNo measures, IL-10 levels, and adverse events (Wanga *et al*, 2019).

Much of the current debate revolves around the relations of the immunomodulatory effect of vitamin D2 in asthma (Al-Sharifi, 2017; Al-Zayadneh *et al*, 2020; Gergen *et al*, 2013; Haider Abdulhameed Alqaraghuli, 2020 and Hall, 2017). Though still contentious, observational and clinical surveys have revealed links between vitamin D2 and BAs (Agrawal, 2017; Al-Zayadneh *et al*, 2020 and Calton *et al*, 2015).

Several inverse causalities may interpret relatively the point that children with BAs be likely to avoid outdoor events, therefore have less exposure to sunlight than those without BAs and subsequent low vitamin D2 concentrations. Still, earlier researches have publicized that even high sun exposure does not warrant sufficient vitamin D2 levels (Vu, 2011).

Low serum vitamin D2 levels may characterize the western lifestyle (Vu LH, 2011). Contemporary life correlates with lower intervals spent outside, altered diet, more obesity, exposure to tobacco smoke, ultrafine molecules, ozone, and poor physical activities. Mutually, such elements are associated with high BA incidence and severity.

Other scholars have exposed that lower vitamin D2 levels are related to decreased respiratory functions, poor control and the presence of exercise-induced bronchospasm of BA patients (Chinellato, 2011a and 2011b). Another study indicated increased values of vitamin D2-binding protein and vitamin D2 in bronchoalveolar lavage secretions following allergen challenge, signifying a contribution for these issues in allergic late-phase response (Bratke, 2014). In contrast, other studies indicate that high serum levels of vitamin D2 may increase the risk of asthma and allergic diseases (Gale, 2008 and Hypponen, 2004). Thus, previous studies on this topic seem to be inconclusive.

Our results of lack of association between BAs and vitamin D2 are fascinating in the milieu of preceding studies. It has been reported that the conversion of inactive vitamin D2 to the active vitamin D2 in the respiratory passages is associated with high levels of the mediators of intrinsic immunity (marked cathelicidin with defensins) that contribute to the prevention of respiratory tract inflammations (Teclé *et al*, 2010) or hurt respiratory muscle function. The viral infections can trigger exacerbations in most BAs subjects (Adeli *et al*, 2019). Hence, it speculated that the maximum effect of vitamin D2 would see with exacerbations (Ali and Nanji, 2017). These anticipated pathways occurred mainly in early life; therefore, vitamin D2 status might be less crucial in adults' BAs.

Another potential explanation of the link between vitamin D2 and BAs in the prior studies is the bias of misclassification of BAs. Furthermore, we estimate that this relation might explain by the consumption of vitamin D2 supplements among asthmatic patients.

Airway remodeling occurring in asthma is characterized by structural changes besides the involvement of inflammatory cells and airway epithelial cells (Berraies *et al*, 2014), which synthesize "tumor growth factor beta-1 (TGF- γ 1)", a profibrotic cytokine with multicellular activities (Fouad Shareef Dleikh, 2020; Hayder AA Al-Hindy, 2020; Mazin J Mousa, 2020). TGF- γ 1 has a prominent influence on Th2-derived cytokines that play a vital role in airway remodeling (Cao *et al*, 2010 and Berraies *et al*, 2014).

A probable clarification for the non-association of serum vitamin D2 with BAs in our study might be the age. Our study included adults aged 28–68years, while most revisions detecting significant associations have concentrated on early childhood and adolescents (Hypponen, 2004; Gale, 2008; Al-Sharifi, 2017 and Al-Zayadneh *et al*, 2020). Other suggested mechanisms of the possible link between vitamin D2 and the development of BAs is that sufficient vitamin levels throughout gestation and early juvenile period inhibit respiratory infections, support pulmonary growth, and hence reduce the risk of BAs (Thuesen *et al*, 2015a).

It is desirable to perform multiple measurements for serum Vitamin D2 for the participants to have more accurate vitamin D2 valuations owing to the vitamin D2

seasonal variation. To have a single measure is a chief limitation of this study. The second limitation is the low sample sizing, which challenges our outcomes to be generalized. Accordingly, further randomized clinical trials are desirable to fully explain the latent relations of vitamin D2 with asthma outcomes.

CONCLUSION

The authors did not report any associations of serum vitamin D2 with the incidence of BAs, despite a significant difference in the distribution of vitamin D2 classes between the well-controlled and the poorly controlled asthma.

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