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Association of High-Sensitivity C-Reactive Protein and Vitamin D with Bronchial Asthma

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Abstract

BACKGROUND: Bronchial asthma (BA) is a common lung illness and a significant health concern globally. Vitamin D (VitD) has immunomodulatory effect able of reducing inflammatory responses in many cells intricate in BA. VitD deficiency has been linked with much inflammation and global worsening of asthmatic patients. C-reactive protein (CRP) is elevated in primary stages of inflammation of BA and high CRP values are observed with impaired pulmonary function.

AIM: This study aimed to evaluate the relationship between serum levels of HSCRP and vitD in patients with asthma.

PATIENTS AND METHODS: This is a case–control study conducted on 127-patients with 113 (sex/aged matching) healthy control. All participants had blood analysis of HSCRP and correlated with FeNo measures. VitD Values were classified as sufficient (>30 ng/ml), insufficient (20–30 ng/ml), and deficient (<20 ng/mL) based on the preceding reference. For statistical analyses, SPSS/23-IBM had used. The outcomes had calculated at a *95% CI* and had assigned as significant. The categorization accuracy of HSCRP, vitD, and FeNo measures had been investigated under the "ROC curves" for asthma prediction

RESULTS: Compared to the control, the mean FeNo levels were significantly higher in asthmatics (p-0.001). VitaminD levels were parallel between the study groups ($p > 0.05$). The mean HSCRP levels were significantly (p-0.03) higher among asthmatics. Around 40% of all participants had lower than normal levels of serum VitD and <10% only revealed deficient levels. There was a positive non-significant correlation of vitD with FeNo results (r-0.067,p-0.54) and negative non-significant (r-0.082,p-0.086) correlation of vitD with HSCRP. ROC-curve analysis showed a significant ability (p-0.001) of FeNo to distinguish asthma, with high accuracy, sensitivity, and specificity. ROC analysis of HSCRP revealed significant ability (p-0.001), but with lower accuracy, sensitivity, and specificity to distinguish asthma patients from healthy subjects. Unlikely, VitD had a non-significant (p-0.085) and lower ability to predict asthma from healthy participants showing AUC, sensitivity, and specificity.

CONCLUSION: No relation or minor conflicting correlations between serum levels of vitD with asthma severity, treatment history, and inflammation (as indicated by HSCRP). Highly sensitive CRP is correlated with asthma.

Introduction

Bronchial asthma (BA) is a common lung illness and a significant health concern affecting over 315 million individuals globally [1], [2], [3], [4]. It continues to be under-evaluated both in diagnoses and treatment, though the lifestyle or environmental variations are potential prominent factors. As a chronic heterogeneous disease, BA involves three main respiratory pathologies: airways hyper responsiveness (AHR), inflammation, and remodeling [5]. The response in BA implicates activation of basic cells and cells of the native and adaptive immunity. Consequently, the produced mediators give rise to inflammatory cells engagement, which eventually induces chronic inflammation [6], [7].

In current years, with the increasing knowledge of diseases, the role of vitamin D (vitD) has also been comprehensively exposed. VitD has pleiotropic effects including bones metabolism, female reproduction, gestational outcomes, neuropsychiatry, and malignancy [8], [9], [10]. In addition, vitD had also been reported to have potential valuable impacts on inflammation and pain alleviation [5], [10], [11]. Vitamin D has a forceful immunomodulatory effect able of reducing inflammatory responses in many cells intricate in BA. Deficiency of vitD has been linked with much inflammation and global worsening of asthmatic patients [12], [13]. Hence, determining the role of vitD in asthma is vital and significant.

Preceding studies had suggested that several diseases might be accompanied by acute or chronic inflammation to some degree [14], [15], [16], [17], [18]. C-reactive protein (CRP) is produced by the liver [18], [19], [20] and had recognized as one of the best inflammatory biomarkers of the acute phase [8], [21]. Of note, CRP is elevated in primary stages of inflammation of BA [7], [8]. High serum CRP values are observed with impaired pulmonary function

and AHR. In asthma, a rapid CRP synthesis serves as a widespread scavenger particle aiding in process of phagocytosis and cellular defense mechanisms [7].

For that reason, it is sensible to explore the role of vitD in BA via its associations with CRP. This comparative study was aimed to evaluate the relationship between serum levels of CRP and vitD in patients with asthma.

Patients and Methods

Sample collection and study design

The study had conducted in Merjan Teaching Hospital in Babylon during the period from August to November 2020 including 127 asthmatic patients with 113 (sex/aged matching) healthy control. The age of the participants ranged from 19 to 59 years. Asthma had diagnosed and assessed by physicians at the hospital, depending on the "Global Initiative for Asthma guidelines (GINA)." Whether patients were on consistent or inconsistent asthma medications, they had grouped into treated and untreated. The FeNo results had obtained in private centers, according to the "guidelines of the American Thoracic Society (ATS)".

Biochemical assays

Highly sensitive CRP (HSCRP) and vitD had estimated by "CALBIOTECH® ELISA kit," and correlated with FeNo measures of all participants. VitD values were classified as sufficient (>30 ng/ml), insufficient (20–30 ng/ml), and deficient (<20 ng/mL) based on preceding reference [22].

Ethical consideration

Informed consent had acquired from each participant separately, and the entire work had agreed on by the local committee for research ethics at the local authorities.

Statistical analysis

Statistical Package for the Social Sciences (SPSS/23-IBM) had used. The Chi-squared test had used for univariate investigation, and a t-test had completed detecting variations between the studied groups, treatment groups, and genders. The outcomes had calculated at a *95% CI* and had assigned as significant for all variables. The categorization accuracy of HSCRP, vitD, and FeNo measures had been investigated under the "ROC curves" for their diagnostic fitness to decide asthma prediction.

Results

Basic characteristics of the studied groups

The mean age of all participants was 34.1 ± 6.9 years, which was parallel in the two groups. The asthmatic patients were heavier than the control subject (p-0.04). The male patients were fewer than females in this study (p-0.003). The asthmatic patients were treated for an average duration of 8.02 ± 3.9 years. Nearly 40% of patients were on a regular antiasthma regimen. Compared to the control group, the mean FeNo levels were significantly higher in asthmatics (p-0.001). Vitamin D mean levels were parallel between the study groups (p > 0.05). The mean HSCRP levels were significantly (p-0.03) higher among asthmatics. Around 40% of all participants had lower than normal levels of serum VitD and <10% only revealed deficient levels (Table 1).

Table 1: Basic characteristics of the studied groups

Study parameter	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 (45.1%)	67 (54.9%)	0.003
	Females (118)	72 (61%)	46 (39%)	
Treatment history	On treatment	53 (41.7%)	0.05	
	Without treatment	74 (58.3%)		
Duration of asthma (years)	8.02 ± 3.9			
FENO (ppb)	28.6 ± 20.1	43.8 ± 29.5	8.9 ± 4.0	0.001
VitD2 (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%)	
HSCRP (mg/L)	4.7 ± 3.8	5.3 ± 8.9	3.3 ± 3.5	0.03

Effect of asthma therapy

The effect of asthma therapy on vitD and HSCRP levels among asthmatic patients is well studied as shown in Table 2. It reveals that no effect of history of the treatment of BA on the blood levels of both variables (p-0.34 and 0.429), respectively.

Table 2: Relationship of Vitamin D2 and HSCRP with history of treatment

	Treatment	Mean ± SD	p-value
VitD2	On	21.9 ± 10.9	0.341
	With out	20.2 ± 5.1	
HSCRP	On	6.4 ± 11.9	0.427
	With out	4.7 ± 6.0	

Correlation of FeNo results with HSCRP and Vitamin D2

There was a positive non-significant correlation of vitD with FeNo results (r-0.067, p-0.54) and negative non-significant (r—0.082, p-0.086) correlation of vitD with HSCRP (Table 3).

Table 3: Correlation of FeNo results with HSCRP and Vitamin D2

	HSCRP	VitD2
FeNo		
Correlation	0.082	0.067
Significance	0.43	0.54
HSCRP		
Correlation	-	-0.082
Significance	-	0.086

ROC curve analysis (Figure 1 and Table 4) of FeNo, vitD, and HSCRP values had performed to inspect their predictability for asthma. It showed a significant ability (p-0.001) of FeNo to distinguish asthma, with high accuracy, sensitivity, and specificity: 0.967, 93.5%, and 93.2%, at 95% CI [0.946-1.000], respectively. Likewise, ROC curve analysis of HSCRP revealed significant ability (p-0.001), but with the lower accuracy (0.881), sensitivity (87.1%), and specificity (76.3%) at 95% CI [0.812–0.950] to distinguish asthma patients from healthy subjects. Unlikely, VitD had a non-significant (p-0.085) and lower ability to predict asthma from healthy participants showing AUC (0.612), sensitivity (54.8%), and specificity (68.3%) at 95% CI [0.488–0.736].

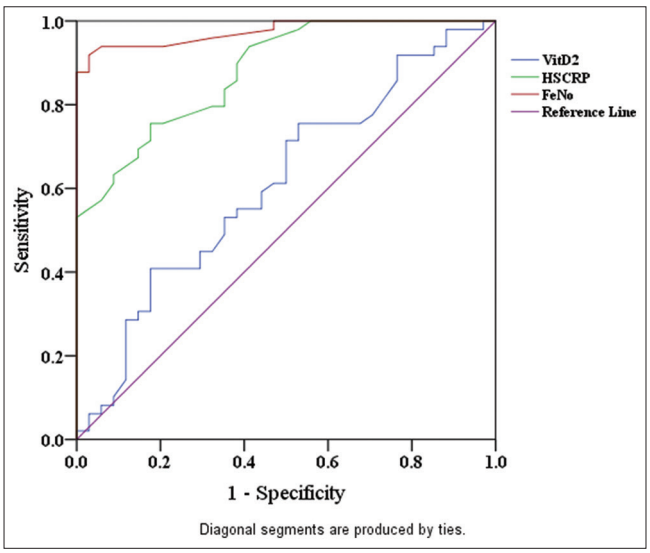

Figure 1: ROC curve for predictive features of VitD, HSCRP, and FeNo for asthma diagnoses

Discussion

In the latter decades exclusively, a cumulative bulk of data emphasized how vitD could control several biological activities; henceforth, vitD was revived being not simply the bones vitamin, but as well, multipurpose vitamin [9]. In this context, several epidemiological studies address the link between vitD and BA [5], [22], and the role of vitD insufficiency in asthma evolvement and exacerbations [23].

Table 4: ROC curve for predictive features of VitD, HSCRP, and FeNo for asthma diagnoses

Variables	AUC	Significance	Specificity (%)	Sensitivity (%)	95% Confidence interval	
VitD2	0.612	0.085	68.3	54.8	0.488	0.736
HSCRP	0.881	0.001	87.1	76.3	0.812	0.950
FeNo	0.975	0.001	93.2	93.5	0.946	1.000

In our group of adults with BA, no correlation between reduced vitD levels and FeNo or HSCRP levels had reported, though HSCRP levels and FeNo index were significantly higher among BA patients compared to the control group. As well, poor ability of vitD for asthma prediction compared to FeNo and HSCRP was found. Supporting our findings, are three pieces of research had conducted on different ages; one conducted in Belgium [24], and two in the USA [25], [26], which had revealed no influential role of vitD in BA.

Our outcomes are intriguing in the context of previous Iraqi studies [27], [28], [29]. Meanwhile, Han *et al*. reported a parallel decreased prevalence of vitD insufficiency in BA in a US national study in 2017 [12]. VitD activates vitD receptor (VDR) and induces an immune modulatory effect on host immune mediators (especially defensins and cathelicidin) [30] or immune cells such as dendritic cells, macrophages, B/T lymphocytes, and besides basic respiratory cells [31].

Vitamin D status is best measured by assessing serum 25-(OH)D as it reflects the peak of all vitD metabolites and has a shelf-life of around 3 weeks [31]. Despite the fortified foods and the multivitamin intakes, few studies have exposed that vitD deficiency is still prevailing in many developing states including sunny zones. An altered lifestyle like sunlight under-exposure, change to indoor activities, sunscreen applications, besides nutritional changes are potential etiologies [32]. In this sense, the fortified foods in present dosages seem insufficient to prevent vitD deficiency. Moreover, deficient vitD levels are multifactorial that include race, gender, polymorphisms or deficient vitD binding proteins or VDRs, and other genetic factors involved in vitD breakdown [5]. Worthy to mention, that subjects with severe BA are expected to spend more hours indoors with less sun exposure, leading to lower serum Vitamin D levels.

Conversely, outcomes from interventional trials were inconsistent and there is still much disagreement as to whether or not vitD supplements present a practical substitute or adjunct therapy for BA. Another cohort had included a wide pediatric asthma group in Costa Rica, failed to display a significant inverse relation of serum vitD with AHR [33]. However, there was no standardization of asthma treatment in this survey. Moreover, a previous study assessing patients with vitD-resistant rickets exhibited protection to the airways hyper-reactivity triggered by methacholine challenge [34].

Secondary studies were piloted in two samples of adolescents in the USA in 2013 revealed a lack of association between serum 25(OH) vitD and BA [30]. In 2015, a Danish study conducted by Thuesen *et al*. shows that vitD levels do not impact the worsening of asthma and atopy among adults [35].

Maternal cord-blood levels of vitD had inverse associations with risk of respiratory infection and childhood wheezing but no association with incident asthma in the children at their later adolescent ages in New Zealand study [36].

Based on the data from the previous studies, a parallel relation between vitD and BA outcomes

could be concluded. Yet, it is confusing to express a relationship between them owing to certain limitations of these surveys including the bias of case selection, other confounders (physical activity, gender, age, and BMI), and different sample sizes. All these limitations could have produced some false relationships between vitD and BA. In addition, all these studies, not without major methodological weaknesses, which limit our sureness in their outcomes. For instance, none of the aforesaid studies applied standardized therapy to exclude treatment variations, besides no study observes seasonal variations among BA patients.

The role of inflammation in AHR is documented by numerous previous scholars [6], [7]. HSCRP is a marker indicating low-grade inflammation [17], [20], [37]. A prior meta-analysis proposed that vitD supplements reduce serum HSCRP concentrations in adults by 1mg/l or more [38]. An anti-inflammatory impact of vitD is a consistent opinion in studies of cell lines and human-derived mononuclear cells [39]. Because vitD might reduce the systemic inflammatory response and protect from BA, this study aimed to evaluate the prevalence of vitD insufficiency with HSCRP among asthmatic patients.

What is more, transforming growth ḟacto-β (TGFβ) is a pleiotrophic-cytokine [40], [41], [42], formed by epithelial respiratory cells and excites fibroblasts growing that may induce excessive fibrosis of pulmonary soft tissue [3]. Prior reviews verified a raised TGFβ1 in obstructing lung illnesses. In addition, both IL-1B and TGFβ adjust T-helper17 cells, which have a serious role in the etiopathology of chronic inflammation. As well, both interleukins and TGFβ can activate platelet derived growth factor (PDGF) release [2], [43]. PDGF is a strong mitogen released by diverse cells like fibroblasts (40) identified to induce an immune-regulatory influence in BA by facilitating remodeling of respiratory airways [2].

The data from this study finding are consistent with the outcomes reported currently [7], [8], which showed a significant correlation of HSCRP with the severity of BA. Interleukins (1 and 6) modify HSCRP and take apart in airway inflammation. High serum HSCRP values are linked with impaired respiratory functions and AHR. In BA, there is a rapid CRP synthesis that serves as a universal hunter particle aiding in processes of opsonization, phagocytosis, and cytotoxicity [7], [44].

In line with the previous studies [8], [45], we found that among asthmatic patients, the levels of vitD in the serum were not associated that of HSCRP. Likewise, an Australian randomized trial of 413 subjects indicated that the relation of CRP with vitD was not significant (46). Earlier reports from tertiary referral centers validated increased serum HSCRP values accompanied asthma exacerbation [7], [8], [44]. Limited revisions concentrated on the non-linear relations between vitD and CRP, and vitD was usually categorized as deficient or not [8], [46]. Yet, the categorical parameter cannot mirror the global distribution of vitD, and cannot fully reveal the associations of HSCRP with vitD.

In BA, and principally in the severe form, several biomarkers have been deliberated; nevertheless, the only restricted number so far can be simply practiced on a clinical base. Unfortunate speaking, currently, an ideal model does not present and there is a real overlay among the biomarkers.

Conclusion

No relation or minor conflicting correlations between serum levels of vitD with asthma severity, treatment history, and inflammation (as indicated by HSCRP). Highly sensitive CRP is correlated with asthma. High-quality extended studies are desirable to reliably answer the inquiry of concern.

Limitation

There were a few limitations in this study. The sample size was small as well as it was not a longitudinal study. All of the asthmatic cases should be evaluated for the control of asthma by using ACT or ACQF according to GINA guidelines. PFT should be used also.

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