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CRP Levels and Vitamin D as Predictors of Asthma Control: A Data-Driven Approach

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Abstract

Background: Asthma is a chronic inflammatory disease of the airways characterized by episodic exacerbations and airflow obstruction. Elevated C-reactive protein (CRP) levels indicate systemic inflammation and are associated with increased disease severity in asthma. Additionally, vitamin D is thought to modulate immune responses and inflammation, potentially influencing asthma control. This study explores the relationships between CRP levels, vitamin D levels, and asthma control, as measured by the Asthma Control Test (ACT).

Objectives: The primary objective of this study was to assess the correlation between CRP levels, vitamin D levels, and asthma control in adult patients with asthma. The study aimed to determine whether CRP and vitamin D could serve as predictive markers for asthma control.

Methods: This single-center, prospective observational study enrolled 40 adult patients with confirmed asthma from the outpatient pulmonary clinic of ESIC Government Hospital, Guwahati, Assam, India. Asthma control was evaluated using the ACT, with scores categorized as well-controlled (ACT $\geq$ 20) or poorly controlled (ACT < 20). Serum CRP and vitamin D levels were measured using the ELISA method. Pearson's correlation coefficient and ANOVA were employed to analyze the relationships between these variables.

Results: The study found a moderate negative correlation between CRP levels and ACT scores (r = -0.58), indicating that higher CRP levels were associated with poorer asthma control. Patients with CRP levels greater than 10 mg/dL had significantly lower mean ACT scores compared to those with lower CRP levels. In contrast, a strong positive correlation was observed between vitamin D levels and ACT scores (r = 0.879), with higher vitamin D levels associated with better asthma control. The ANOVA test revealed significant differences in ACT scores across different vitamin D and CRP categories ($p < 0.05$).

Conclusions: The study suggests that elevated CRP levels are indicative of poorer asthma control, while higher vitamin D levels are associated with better control of asthma. CRP and vitamin D levels may serve as valuable biomarkers for assessing asthma severity and guiding treatment strategies. However, the variability in response to vitamin D supplementation highlighted the need for personalized approaches to asthma management. Further research is required to confirm these findings and explore the underlying mechanisms.

Keywords: Asthma, C-reactive protein, Vitamin D, Asthma Control Test, Inflammation, Biomarkers

Introduction

Asthma is a chronic inflammatory disease of the airways characterized by recurrent wheezing, breathless-

ness, chest tightness, and coughing. It involves complex interactions between genetic predisposition and environmental factors, leading to airway hyper-responsiveness and airflow obstruction[1]. The pathophysiology of asthma includes chronic inflammation, which is driven by a variety of immune cells and mediators, resulting in structural changes and airway remodeling[1].

Elevated CRP levels indicate systemic inflammation and it's raised in infections and autoimmune diseases[2]. Raised CRP is also closely linked to asthma exacerbations, airway obstruction, and overall disease severity[3]. Researching CRP levels in asthma is vital for several reasons as understanding systemic inflammation's role in asthma can enhance knowledge about the disease's underlying mechanisms. Identifying the relationship between CRP and asthma could lead to the development of specific anti-inflammatory therapies. CRP levels can help tailor individualized asthma management strategies and could serve as a biomarker for tracking disease progression and treatment effectiveness.

The interest in vitamin D as a potential modulator of asthma stems from several observations. It enhances the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10), and inhibits the production of pro-inflammatory cytokines, such as interleukin-17 (IL-17) and tumor necrosis factor-alpha[4] (TNF-α). Research has demonstrated that lower serum 25(OH)D levels are associated with a higher prevalence of asthma, increased hospitalizations, more frequent emergency room visits, reduced lung function, and heightened airway hyper-responsiveness in children with asthma.[5,6]

The study uses a data-driven approach to assess these relationships, aiming to enhance asthma management strategies by considering vitamin D and CRP levels as potential factors influencing asthma severity and control.

Materials and Methods

Study design

It was a single-center prospective observational study.

Data Collection

The study patients were derived from patients with asthma presented in examination in the outpatient pulmonary clinic of ESIC Government Hospital Guwahati Assam India. We enrolled adults (18 yrs. of age or older) with a clinical history of asthma confirmed by bronchodilator responsiveness improvement in $FEV_1 \geq 12\%$ (and ≥ 200 ml) after inhalation of a short-acting β_2-agonist defined by the American Thoracic Society[7]. Those included were nonsmokers, no history of vitamin D supplementation, and had no history of pulmonary tuberculosis. Those with bronchiectasis, pulmonary infection, connective tissue diseases, vasculitis, coexistent acute or chronic localized or systemic infection, or inflammatory conditions, and patients with malignancies were excluded. All participants gave informed consent and the proposal of this study was approved by the Ethics Committee of ESIC Govt Hospital Guwahati Assam. The level of control of asthma was determined using ACT. The patients were classified as, well-controlled or poorly controlled according to ACT score of ≥ 20 or < 20 respectively[8]. Serum CRP and vitamin D were measured by the ELISA method.

Sample size

To calculate the sample size for estimating a prevalence, we can use the formula for sample size calculation for proportions $n=Z^2.\ p.(1-p)/E^2$. Where n is the sample size. Z is the Z-score, corresponding to the desired confidence level. p is the estimated prevalence. E is the margin of error. The Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in Adults (INSEARCH) estimated the national burden of asthma at 17.23 million with an overall prevalence of 2.05%[9]. Using a

confidence level of 95% corresponds to a Z score of 1.96 and a margin of error of 5% or 0.05. The calculated sample size is 30.12. For a better representation, we concluded with a final sample size of 40 patients.

Statistical Methods Used in the Analysis

The central tendency and variability of vitamin D levels, ACT scores, and CRP levels are described using means and standard deviations. The strength and direction of the linear relationship between vitamin D levels and ACT scores, as well as between CRP levels and ACT scores, are assessed using the Pearson correlation coefficient (r). A scatter plot is used to visually represent the relationship between vitamin D levels, ACT scores, and CRP levels and ACT scores. A trend line (regression line) is fitted to the scatter plot to illustrate the overall trend. ANOVA Test is used to determine if there are statistically significant differences in mean ACT scores between the different vitamin D categories and CRP categories.

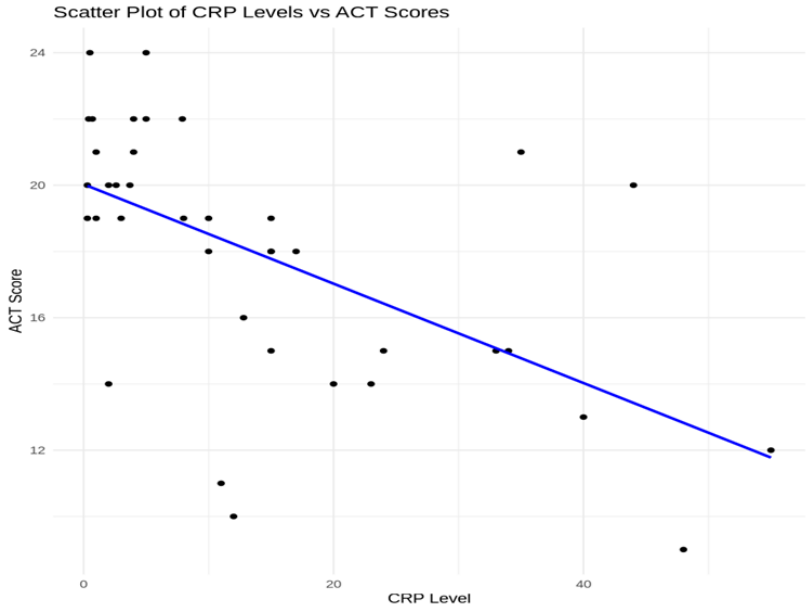
Software and Tools

All statistical analyses were performed using R version 4.0.5, a software environment for statistical computing and graphics.

Results

CRP and ACT score

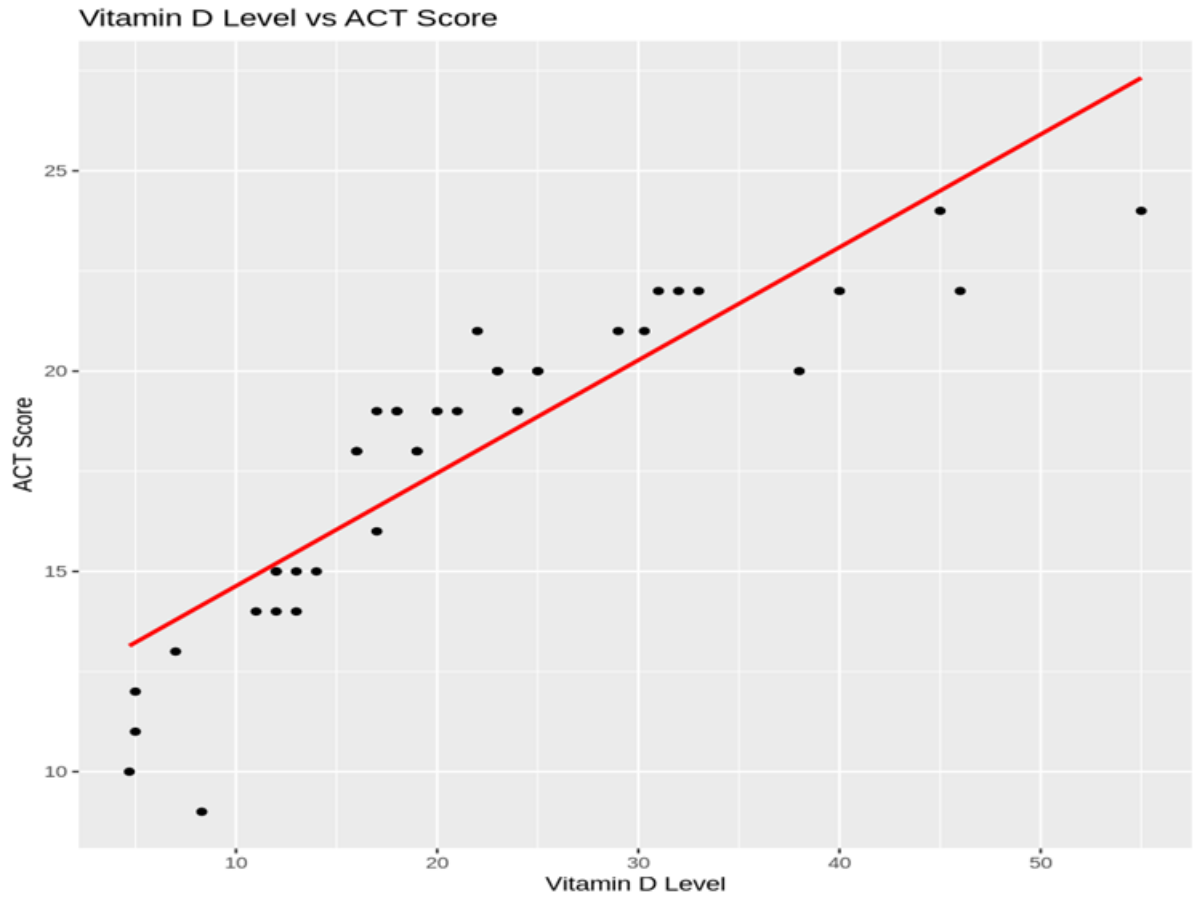
The mean CRP level is approximately 14.22 mg/dL, with a standard deviation of approximately 14.91 mg/dL. To perform a categorical analysis of CRP levels with ACT scores, we need to categorize the CRP levels and analyze the ACT scores within each category. We'll use the existing categories for CRP levels from the dataset: <1-5 mg/dL, 5-10 mg/dL, and >10 mg/dL. Here is the analysis of the mean ACT scores based on the CRP categories, CRP level <1-5 mg/dL: Mean ACT score = 20.56, CRP level 5-10 mg/dL: Mean ACT score = 16.00, CRP level >10 mg/dL: Mean ACT score = 15.93. The ANOVA test results show that the p-value for different categories of CRP levels with ACT scores is approximately 0.0073. This indicates a statistically significant difference in ACT scores across different CRP-level categories. The correlation coefficient for the relationship between CRP levels and ACT scores is approximately -0.58. This indicates a moderate negative correlation, suggesting that ACT scores decrease as CRP levels increase. Here is the scatter plot of CRP levels vs ACT scores with a trend line. The blue line represents the linear trend, showing the negative correlation between CRP levels and ACT scores. (Fig.1)



The regression equation for the relationship between CRP levels and ACT scores is, ACT score=20.02732−0.15002×CRP level. This equation indicates that for each unit increase in CRP level, the ACT score decreases by approximately 0.15002 points.

Vitamin D and ACT Scores

The mean vitamin D level is approximately 21.56 ng/mL, with a standard deviation of 11.99 ng/mL. The mean ACT score is about 17.89, with a standard deviation of 3.85. The strong positive correlation with a correlation coefficient of 0.879 suggests that higher vitamin D levels are associated with higher ACT scores in this dataset. The scatter plot shows a clear positive trend between vitamin D levels and ACT scores. Each point represents an individual in the dataset, and the red line is the linear regression line, which helps to illustrate the overall trend. (Fig.2). The vitamin D levels have been categorized as follows, **Deficient**: Vitamin D level < 20, **Insufficient**: Vitamin D level between 20 and 30, **Normal**: Vitamin D level >= 30. Here are the mean ACT scores for each vitamin D category, Deficient: 15.1, Insufficient: 19.89, Normal: 22.11. The ANOVA test results show a significant difference in ACT scores between the vitamin D categories with a p-value of 1.5×10^{8}. This indicates that the differences in mean ACT scores between the groups are statistically significant.



Discussion

The significance of airway inflammation in asthma is well-recognized. CRP can activate macrophages by interacting with Fc receptors for antibodies[10] and directly act on monocytes and neutrophils by recognizing CRP-R receptors on their surface[11]. Given that hs-CRP is an easily obtainable and relatively low-cost blood test, it could serve as a surrogate marker for airway inflammation in a resource-limited setting like India.

The study also examined the relationship between CRP levels, a marker of systemic inflammation, and ACT scores. We found a moderate negative correlation (r = -0.58) between CRP levels and ACT scores, indicating that higher CRP levels are associated with poorer asthma control. This is consistent with previous studies that have identified elevated CRP levels as indicative of increased inflammation and worse asthma outcomes.

The categorical analysis of CRP levels showed that patients with lower CRP levels (< 5 mg/dL) had significantly higher mean ACT scores, suggesting better asthma control compared to those with higher CRP levels (> 10 mg/dL). The ANOVA test confirmed a statistically significant difference in ACT scores across different CRP level categories (p = 0.0073).

The negative correlation between CRP levels and ACT scores supports the potential role of CRP as a biomarker for asthma severity and control. Elevated CRP levels may reflect ongoing systemic inflammation that exacerbates asthma symptoms and reduces lung function. These findings align with previous research indicating that higher CRP levels are observed in patients with poorly controlled asthma and that CRP levels can serve as a predictor of asthma exacerbations.

Significant evidence supports the effect of serum C-reactive protein (CRP) levels in asthma patients. A case-control study investigated serum C-reactive protein (CRP) levels in patients with asthma compared to a control group. They found that patients with poorly controlled asthma had significantly higher CRP levels compared to those with well-controlled asthma and the control group[12]. The researchers noted a correlation between elevated CRP levels and disease severity and airflow limitation, indicating that CRP might be a useful marker for assessing asthma control and severity[3]. In another study performed on children with asthma of various severity degrees (mild persistent, moderate persistent, and severe persistent), hs-CRP, gradually increased from mild to moderate and severe[13].

Our study establishes the relationship between vitamin D levels and various indicators of asthma control and inflammation among asthma patients. The primary findings unequivocally demonstrate a strong positive correlation between vitamin D levels and Asthma Control Test (ACT) scores, conclusively suggesting that higher vitamin D levels are associated with better asthma control. The ANOVA test further supported this association by showing a significant difference in ACT scores between the vitamin D categories (deficient, insufficient, and normal). Patients with normal vitamin D levels (≥ 30 ng/mL) had the highest mean ACT scores, suggesting better asthma control than those with deficient or insufficient vitamin D levels.

Vitamin D supplementation can lessen asthma exacerbations, especially in children. Several well-documented RCTs[14,15-18] supported this claim. Higher vitamin D levels were associated with greater lung function. There was an increase in FEV_1 for each nanogram per milliliter increase in vitamin D. Participants with vitamin D insufficiency (<30 ng/ml) demonstrated increased airway hyperresponsiveness.[19]

In contrast, studies evaluating vitamin D and its effect on asthma control test scores revealed conflicting results. An analysis of three RCTs reporting Asthma Control Test (ACT) scores[20,16,21], which included a total of 526 participants, revealed no significant difference in ACT scores between those receiving vitamin D supplementation and those receiving a placebo. This indicates that vitamin D supplementation did not result in a statistically significant improvement in asthma control as measured by ACT scores across these studies contrary to our findings.

Conclusion

Our study underscores the potential importance of monitoring vitamin D and CRP levels in asthma management. Higher vitamin D levels are associated with better asthma control, while higher CRP levels are linked to poorer control. However, the study also highlights the need for further research to understand the underlying mechanisms and establish causal relationships. Clinicians should consider these factors as part of a comprehensive asthma management strategy, but should also be aware of the variability in individual responses and the need for personalized approaches to treatment.

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