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Relationship between fractional exhaled nitric oxide, asthma control test, and spirometry measurement in individuals with asthma receiving treatment

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Abstract

To evaluate the relationship between fractional exhaled nitric oxide (FeNO), asthma control test (ACT), and spirometry measurements in individuals with asthma receiving treatment, a cross-sectional study was conducted involving 47 diagnosed asthmatic patients. FeNO levels were measured using Eversens Evernoa FeNO, ACT scores were recorded, and spirometry (pre- and post-bronchodilator) was conducted. Correlations between these parameters were analyzed using Pearson's correlation and t-tests. The study found no statistically significant correlation between FeNO and spirometry parameters [forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and FEV1/FVC] or ACT scores. While FeNO was higher in individuals without a family history of asthma and nonsmokers, these differences were not statistically significant. Additionally, spirometry parameters showed significant improvement after bronchodilator use, but FeNO did not strongly predict lung function improvement. The findings suggest that while FeNO is useful as an indicator of airway inflammation, it may not consistently correlate with functional lung measurements or asthma control as assessed by spirometry and ACT. This highlights the need for a multidimensional approach to asthma management that combines these tools for more comprehensive disease assessment.

Key words: asthma, fractional exhaled nitric oxide, spirometry, asthma control test, airway inflammation.

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Introduction

Chronic airway inflammation, or asthma, is characterized by hyperreactivity in the body and recurring episodes of coughing, chest tightness, or wheezing in the clinic. The underlying pathophysiology of asthma includes mucus hypersecretion, bronchial hyperresponsiveness, mucosal edema, smooth-muscle contraction, and airway inflammation [1].

A chronic inflammatory illness of the respiratory tract, bronchial asthma is brought on by the production of several inflammatory mediators by mast cells, eosinophils, and T lymphocytes. In bronchial asthma, airway obstruction is primarily brought on by the following four mechanisms: i) irreversible alterations in the lungs (referred to as "remodeling"); ii) edema of the airway walls; iii) mucous clogging of the bronchioles; iv) contraction of the bronchial smooth muscle A significant public health issue that affects a lot of people of all ages is bronchial asthma. Guidelines for asthma diagnosis and assessment include fractional exhaled nitric oxide (FeNO), the Asthma Control Test (ACT), and spirometry [2] (Figure 1).

The quantifiable, non-invasive, straightforward, and safe approach of monitoring airway inflammation known as FeNO concentration in exhaled breat serves as a useful adjunct to other methods of evaluating airway diseases, such as asthma [3].

Human breath contains nitric oxide (NO), which is a sign of inflammation in the airways. Type 2 asthma sufferers exhale more NO, and FeNO is an objective standard of airway inflammation. FeNO testing is an easily available, non-invasive test. The National Institute for Health and Care Excellence, the Global Initiative for Asthma (GINA), and the American Thoracic Society have all determined cut-off levels, although they differ among guidelines. High levels in asthmatic individuals can aid in predicting responsiveness to inhaled corticosteroids (ICS) and ICS-induced level suppression was used to measure adherence.

FeNO testing can improve the diagnostic accuracy of asthma. FeNO levels have a developing function in predicting responsiveness to several biologics therapies in severe asthma. They are also a medium of asthma risk, with high levels linked to greater exacerbation rates and a faster decrease in lung function [4].

The current GINA recommendations highlight the necessity of assessing asthma control in order to inform decisions about asthma treatment. In controlled trial settings, most patients can attain and maintain the level of asthma control recommended by guidelines. To satisfy this need, the ACT questionnaire, a quick, easy, and self-administered evaluation instrument, may be suitable [5].

To assist in making clinical decisions about the management of asthma, doctors constantly take asthma severity and control into account. In addition to using the GINA criteria, the most common method for evaluating asthma control is the ACT questionnaire, which has been proven to be effective. In order to assess FeNO

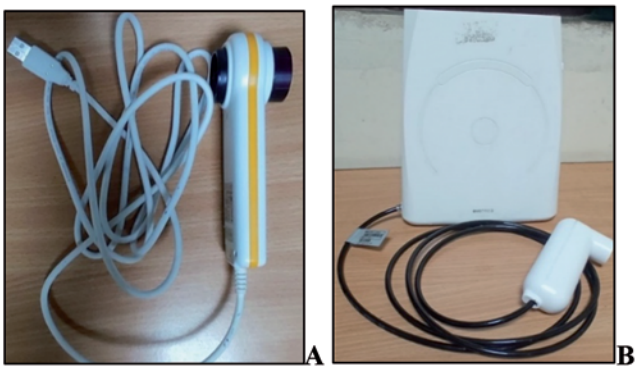


Figure 1. A biomarkers of airway inflammation. A) Fractional exhaled nitric oxide; B) a lung function test measuring forced expiratory volume in 1 second and forced vital capacity.

contribution to asthma treatment, the link between FeNO and asthma severity and control was examined. FeNO was found to be associated with both the ACT score and spirometry parameters [6].

One of the most accessible and practical diagnostics for pulmonary function is spirometry. It measures the following parameters that includes, forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV1), FEV1/FVC ratio, and forced expiratory flow 25-75% (FEF25-75%) [7].

Although previous studies have individually evaluated these parameters, the correlation between them remains inadequately explored, especially in the context of treated asthma. The study's purpose is to assess and compare the ability of FeNO, spirometry, and ACT to predict future asthma exacerbations, as well as their interrelationship. This could lead to more personalized and effective treatment plans by integrating objective (FeNO and spirometry) and subjective (ACT) assessments.

Materials and Methods

Study population

Diagnosed asthmatic patient with the help of spirometry according to GINA 2024, who attended the pulmonary medicine opd of Mahatma Gandhi medical college research institute, were included in this study.

Type of study

Cross sectional study

Duration of study

January 2024 to October 2024

Sample size

The mean FeNO was 29.5±(24.4) from previous research taking α=0.05, precision =5, and the sample size =47.

$$n = \left(\frac{Z\sigma}{E}\right)^2$$

Here, σ=24.4, Z=1.96 and E=7.

Statistical analysis

Continuous variables are presented as mean and standard deviation. The categorized variable will be described with frequency and percentage. A p-value ≤0.05 was considered statistically significant.

Inclusion criteria were: i) diagnosed asthmatic patients with spirometry-FEV1/FVC % ≥LLN, FEV1 change and 200 mL bronchodilator reversibility; ii) consented to participate in the study.

Exclusion criteria were: i) patient with other respiratory diseases (chronic obstructive pulmonary disease, bronchiectasis, pulmonary tuberculosis, upper respiratory tract infection, interstitial lung diseases); ii) co-existing lung infection; iii) patient with respiratory failure; iv) recent myocardial infarction; v) not consented to participated in this study.

Results

In a comparison of FeNO and pre- and post-spirometry parameters and ACT, FVC in the pre- spirometry test and FeNO had a weak negative association (r=-0.216), and there was no statistically significant relationship (p = 0.145). If FVC increases, FeNO will decrease. Likewise, there was a non-significant weak negative correlation (r=-0.206, p=0.165) between FeNO and FEV1 in the PRE spirometry test. Hence, FEV1 in the pre-spirometry test increases, and FeNO will decrease. There was essentially no correlation (r=0.002) between the ratio of the FEV1/FVC-PRE spirometry test and FeNO, suggesting that there was no linear relationship between the two variables (p=0.988). A weak negative association (r=-0.208) was seen between FENO and the small airway function marker FEF25-75 in the pre-spirometry test; however, this link was not statistically significant (p=0.161) (Table 1).

In comparison of FeNO and post-spirometry parameters: The associations between the FVC-post-spirometry test (r=-0.159, p=0.287) and FEV1-post (r=-0.150, p=0.313) and FeNO remained slightly negative and non-significant following bronchodilator administration.

Table 1. Correlation of fractional exhaled nitric oxide and pre- and post-spirometry parameters and asthma control test.

Pre FeNO	FVC Pre	Pre	FEV1-FVC	FEF25-75 pre	ACT
Correlation	-0.216	-0.206	0.002	-0.208	-174
p	0.145	0.165	0.988	0.161	0.242
Sample size	47	47	47	47	47
Post FeNO	**FVC post**	**FEVI post**	**FEV1-FVC post**	**FEF25-75 post**	**ACT**
Correlation	-0.159	-0.150	0.023	-0.092	-0.174
p	0.287	0.313	0.879	0.540	0.242
Sample size	47	47	47	47	47

FeNO, fractional exhaled nitric oxide; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; FEF25-75, forced expiratory flow 25-75%; ACT, asthma control test.

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There was no link indicated by the nearly zero correlation (r=0.028, p=0.879) between the FEV1/FVC-POST ratio and FeNO. Hence, if the FEV1/FVC post-spirometry test increases, FeNO also increases. A weak positive association (r=0.092) was found between FEF25-75 POST and FeNO; however, this result was not statistically significant (p=0.540) (Table 1).

When comparing FENO and ACT, it showed a slight, negative connection (r=-0.174) with a p-value of 0.242. Hence, there was no statistically significant correlation, but greater FeNO readings may be linked to lower ACT scores (poor asthma control) (Table 1).

When correlating the severity of FeNO, ACT, and spirometry, no significant correlation was found between FeNO levels and asthma severity as measured by ACT or spirometry in this sample (p>0.05). However, a trend was observed, with the very poorly controlled ACT category showing higher FeNO levels (Table 2).

Discussion

The correlation study between lung function measurements, FeNO, and ACT provide important insight into the relationship between pulmonary function, airway inflammation, and asthmatic patient's ability to manage their symptoms. Nevertheless, the study's findings showed only modest associations, not statistically significant ones, between FeNO and the ACT score or any of the lung function indicators (FVC, FEV1, FEV1/FVC, and FEF25-75) [8].

The findings indicate that there may not be a direct association between lower lung capacity and higher levels of airway inflammation as evaluated by FENO. This is supported by the slight negative correlation between FENO and FVC both pre- and post-bronchodilator (r=-0.216, p=0.145, and r=-0.159, p=0.287). In a similar vein, weak negative correlations were also seen between FENO pre- and post-bronchodilator (r=-0.206, p=0.165 for pre-bronchodilator; r=-0.150, p=0.313 for post-bronchodilator), and also FEV1 pre- and post-bonchodilator (r=-0.206, p=0.165 and r=0-.150, p=0.313) a measure of airflow obstruction. However, these correlations were not statistically significant. The aforementioned suggests that FeNO, which is predominantly a measure of eosinophilic inflammation, would not accurately reflect the extent of airflow obstruction often seen in individuals with asthma.

One interesting finding is that there was essentially no correlation between FENO and the FEV1/FVC ratio, which measures airflow obstruction (r=0.002, p=0.988 pre-bronchodilator; r=0.028, p=0.879 post-bronchodilator).Weak, non-significant associations were also observed between FeNO and FEF25-75, a measure of small airway function, suggesting that FeNO levels may not be a useful means to quantify small airway inflammation.

Additionally, a weak negative connection (r=-0.174, p=0.242) has been shown between FeNO and the ACT score, indicating that, although not statistically significant, higher levels of airway inflammation may be correlated to worse asthma management. Symptom perception, reaction to environmental stimuli, and the existence of airway hyper reactivity are some of the variables that affect asthma management as measured by the ACT score, in addition to airway inflammation. There is probably less of a correlation between FeNO and ACT because asthma is a complicated multivariate illness [9].

A previous study Smith *et al.* found a moderate connection between FeNO and pre-bronchodilator FEV1 (r=-0.45), indicating that greater FeNO levels were associated with considerably impaired lung function [10]. However, in this study, this connection was weaker and non-significant (r=-0.206, p=0.165), indicating a less prominent correlation between airway inflammation and lung function and another study Shaw *et al.* discovered a significant association between FeNO and post-bronchodilator FEV1 in patients with eosinophilic asthma, indicating that FeNO was an accurate predictor of lung function improvement in the bronchodilator usage [9]. In our investigation, the association was weak and non-significant (r=-0.150, p=0.313), indicating that FeNO did not strongly predict bronchodilator responsiveness.

Pijnenburg *et al.* found a stronger negative connection (r=-0.40) between FeNO and ACT scores, indicating that greater FeNO levels were associated with poorer asthma control [11]. This study, however, reported a weaker and non-significant connection (r=-0.174, p=0.242), indicating that FeNO had a less significant impact on asthma control in our cohort. Another study shows Malinovschi *et al*. discovered a positive correlation between FeNO and FEF25-75% (r=0.38, p<0.01), suggesting that greater FeNO levels are linked to improved small airway performance. This study shows that in some groups, FeNO can reflect minor airway irritation, resulting in improved lung function [12]. However, in our investigation, the connection between FeNO and FEF25-75% was weak and non-significant both pre- and post-bronchodilator (r=-0.208, p=0.161 and r=-0.092, p=0.540). This suggests that FeNO did not have a strong correlation with small airway function in our cohort, probably due to variances in asthma phenotypes or levels of inflammation in the small airways.

The lack of significant findings in post-bronchodilator measures in this investigation is consistent with earlier research. Bronchodilators primarily relieve bronchoconstriction, which is

Table 2. Correlate the severity of fractional exhaled nitric oxide, asthma control test and spirometry.

	FeNO			Total, n (%)	p
	Normal, n (%)	Intermediate, n (%)	Severe, n (%)		
ACT severity					
Well controlled	6 (50.0)	9 (36.0)	2 (20.0)	12 (36.2)	0.321
Not well controlled	2 (16.7)	9 (36.0)	2 (20.0)	13 (27.7)	
Very poorly controlled	4 (33.3)	7 (28.0)	6 (60.0)	17 (36.2)	
Total	12 (100.0)	25 (100.0)	10 (100.0)	47 (100.0)	
Spirometry severity					
Mild	9 (75.0)	19 (76.0)	4 (40.0)	32 (68.1)	0.244
Moderate	1 (8.3)	4 (16.0)	4 (40.0)	9 (19.1)	
Severe and very severe	2 (16.7)	2 (8.0)	2 (20.0)	6 (12.8)	
Total	12 (100)	25 (100)	10 (100)	47 (100)	

ACT, asthma control test; FeNo, fractional exhaled nitric oxide.

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reflected in improved lung function but not necessarily in FENO levels, since FeNO measures airway inflammation rather than bronchoconstriction. This shows that FeNO and bronchoconstriction represent distinct components of asthma pathogenesis. However, there are no significant findings; one interesting data point is that the ACT very poorly regulated severity group is associated with an increased FeNO level group. The reason may be increased FeNO levels are often associated with eosinophilic airway inflammation, which is prevalent in individuals with poorly controlled asthma.

In conclusion, the weak correlations found in this study, as well as comparisons to other negative studies, highlight the complexity of asthma. FeNO is an important marker for airway inflammation; it may not strongly correlate with lung function or asthma control in a straightforward manner.

These findings highlight the importance of a multidimensional approach to asthma therapy, which includes both physiological and symptomatic parameters to provide a comprehensive picture of disease control. Future studies with bigger sample sizes and various demographics may shed light on the link between FeNO, lung function, and asthma control.

Conclusions

In conclusion, neither FeNO nor asthma control (ACT score) was shown to be substantially connected with lung function parameters (FVC, FEV1, FEV1/FVC, and FEF25-75) using Pearson correlation analysis. Particularly in ACT, very poorly controlled severity is associated with increased FeNo levels. These findings suggest that, while FeNO is useful as an indication of airway inflammation, it may not consistently correspond with functional measures of lung function or the management of asthma symptoms in this population. The limitations of the study are its small, cross-sectional sample, preventing robust conclusions about causal relationships and generalizability. Additionally, the reliance on subjective self-reporting (ACT) and single-point FeNO measurements introduces potential variability and bias. Future research may consider additional variables, such as the kind of inflammation or severity of the illness, which may influence the relationship between these traits. This may also involve using a larger sample size to increase the statistical power of the findings.

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Conflict of interest: the authors declare no conflicts of interest related to this study.

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Informed consent: written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article. The manuscript does not contain any individual person's data in any form.

Patient consent for publication: not applicable.

Availability of data and materials: all data underlying used and/or analysed during the current study are available from the corresponding author on reasonable request.

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