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RESEARCH ARTICLE

Assessment of asthma control in adult patients by Fractional Exhaled Nitric oxide and Asthma Control Test

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ABSTRACT

Background: The most crucial step in achieving and keeping asthma under control is to lessen the inflammation in the airways. Nitric oxide fractional exhaled (FeNO) levels have been utilized as an indicator of airway inflammation. Uncertainty regarding the potential function and properties of exhaled fractional nitric oxide in asthma management.

Objective: To determine whether FeNO and Asthma Control Test (ACT) can objectively assess asthma control in adult patients and identify any potential relationships between FeNO and both the ACT score and the spirometry data of patients. Also, determine their use in reducing the dose of inhaled steroids.

Methods: The design of the study was a systematic review. A qualitative research methodology based on an analysis of previously published materials.

Results: This study thoroughly examined the literature on the Asthma Control Test and Fractional Exhaled Nitric Oxide assessment of asthma control in adult patients. Finally, 16 scientific studies were analyzed. The highest variations in FeNO values during diagnosis were significantly linked with FeNO levels at diagnosis during conventional asthma treatment. Evaluating adherence and FeNO response to monitored inhaled corticosteroid treatment may prevent the needless progression to biologic therapy in asthmatic patients with high Type-2 biomarker levels. There is a close connection between the ACT score and the treatment modifications as well as the measurements of lung function. FeNO may be able to detect poor asthma control; however, it cannot substitute for clinical judgment and may only be beneficial in a subset of asthmatics. The average and percentage variation of standards following asthma treatment did not show any significant relationship between FeNO levels and various other factors are related (expiratory volume in one second (FEV1) or ACT scoring), however, there were strong positive correlations between ACT scores and FEV1.

Conclusion: Research revealed a highly significant link between the level of FeNO at diagnosis and the biggest variations in FeNO readings after diagnosis. Using FeNO as a supplementary non-invasive method for assessing asthma control may be effective in both steroid-naive asthmatics and those who are being treated with steroids.

Key Words: Asthma, FeNO, Asthma control test

Introduction

The most prevalent chronic non-communicable disease, asthma is characterized by a history of respiratory problems, including chest tightness, coughing, wheezing, and shortness of breath, together with variable expiratory airflow limitation. It is a heterogeneous disease, usually characterized by chronic airway inflammation and associated with airway hyperresponsiveness to direct or indirect stimuli. Both the respiratory symptoms and airflow limitation characteristically vary over time and in intensity. These variations are often triggered by factors such as allergen or irritant exposure, change in climate, exercise, or respiratory infections[1,2]. It has a severe unfavorable effect on the quality of life, mortality risk, and direct and indirect costs, especially challenging for patients to control asthma[3].

Asthma affects 1–18% of the population in different countries. More than 12% of people in the United Kingdom (UK) have an asthma diagnosis, whereas 5.4 million people receive treatment for this illness, as per the "British Lung Foundation (BLF), 2018"[4]. The "National Health Service" Spends almost £3 billion annually on conditions connected to asthma[4]. Moreover, all age groups are affected by this major worldwide health issue. 276 suspected asthma fatalities were thoroughly evaluated by the confidential inquiry panels in the National Review of Asthma Deaths UK, which evaluated all mortalities registered between February 2012 and January 2013. One of the main conclusions was that just 16% of patients in primary and secondary care were considered to be receiving good care, and 46% of fatalities were preventable[5].

The pathophysiology of asthma is characterized by underlying inflammation of the airways in conjunction with structural changes together known as airway remodeling. Asthma management decisions are typically based on measures of airflow obstruction, the incidence of day or nighttime symptoms, and the frequency of exacerbations. Individuals with persistent respiratory problems or with airflow obstruction at lung function testing and/or who experience asthma exacerbations are classically treated with controller medications such as inhaled corticosteroids (ICSs) with or without a long-acting β-agonist or other medications. Once the diagnosis of asthma is established, selecting the type of therapy and selecting the optimal dose of therapy for the patient are challenging decisions faced by clinicians. Treatment is adjusted based on the level of asthma control that is achieved with the selected therapy; however, the response to therapy is heterogeneous. Biologic therapies targeting specific inflammatory pathways are considered in individuals with uncontrolled asthma.

Asthma immunological phenotypes are complex with differing clinical and inflammatory characteristics. Recognizable clusters of demographics, and clinical or pathophysiological characteristics are often called 'asthma phenotypes'. In patients with more severe asthma, phenotype-guided treatments are available. Thus, there is an increasing need for biomarkers with predictive and prognostic value for the progression of asthma, and their association with available treatments. One phenotype of severe asthma is related to type 2 inflammation, found in approximately half the people with severe asthma. Type 2 inflammation is characterized by the release of cytokines such as interleukin (IL)-4, IL-5, and IL-13 from cells of both the innate and adaptive immune systems acting on the respiratory epithelium and other stromal cells, often on recognition of allergens. The presence of eosinophils also characterizes type 2 inflammation[6].

Making the diagnosis of asthma in a patient is based on identifying both a characteristic pattern of respiratory symptoms and variable expiratory airflow limitation. But in mild to moderate asthma, airway obstruction is frequently absent during spirometry study, increasing diagnostic confusion. Worldwide guidelines advise serial peak-flow monitoring or bronchial stimulation test[7]. Peak-flow variability has, however, already been shown to have a limited diagnostic value[8]. Thus, if spirometric data are inconclusive, bronchial provocation is a test that gauges how sensitive airways are the benchmark for identifying bronchial hyper-responsiveness. However, bronchial Provocations require a lot of time, are expensive, and are frequently available only in particular lung functioning laboratories, and they also carry the danger of severe bronchospasm[9].

The crucial elements of asthma recommend-dations are monitoring tools to help with better asthma management and prevention of asthma attacks. A single outcome cannot accurately

measure the control of asthma. Typically, subjective measurements consist of a series of diary cards, clinical assessment questions, and quality of life surveys[10]. Peak flow, spirometry, and the level of airway hyperresponsiveness (AHR) are among the major objective techniques used to observe but not to treat asthma. Studies have indicated that the goal of asthma care is to reduce persistent inflammation while enabling patients to attain and maintain asthma control. Th2-driven inflammation, commonly known as eosinophilic inflammation, is the main inflammatory mechanism in asthma[11]. Biomarkers that reflect the pathophysiological mechanisms involved in type 2 inflammation-driven asthma include fractional exhaled nitric oxide (FeNO), serum IgE, serum periostin, and blood and sputum eosinophils.

People with asthma might have predominately eosinophilic or non-eosinophilic inflammation of the airways, including neutrophilic inflammation. Inhaled corticosteroids (ICS) continue to be the principal preventive therapy for controlling asthma symptoms[12]. In contrast to patients with neutrophilic inflammation, eosinophilic inflammation patients recover better from ICS for symptom control. Inhaled corticosteroids, an anti-inflammatory drug that appears to improve the outcome of asthma by reducing eosinophilic airway inflammation[13]. Therefore, studies that offer accurate information about eosinophilic inflammation may help to reduce exacerbations and enhance asthma management.

Exhaled nitric oxide levels are measured with FeNO devices. Nitric oxide fractionally exhaled (FeNO) can be used to analyse bronchial asthma. Nitric oxide is used as a diagnostic tool for asthma since it reflects the severity of respiratory inflammation[14]. FeNO is a non-invasive signal that may be used to predict the efficacy of standard corticosteroid and biologic therapy in specific patient groups and to identify specific asthma morphologies, such as eosinophilic asthma. Nitric oxide exhalation production is measured using FeNO devices on sufferers. Nitric oxide is measured in the exhaled air using a portable equipment that measures the concentration in parts per billion (PPB). FeNO testing generates a FeNO score that quantifies the amount of inflammation[14]. Concentrations of FeNO below 25 ppb are regarded normal, whereas those between 25 and 50 ppb are deemed high.

Elevated concentrations of inducible nitric oxide synthase (NOS2) enzyme expression in the epithelial cells of asthmatic patients' airways and high amounts of nitric oxide in their exhaled breath suggests a role for the physiology of the disease and nitric oxide[15]. Over the past 15 years, the study of exhaled nitric oxide measurement has advanced dramatically. It was discovered that high FENO concentrations were found in the exhaled breath of asthmatic patients which dropped in response to corticosteroid treatment[16]. The assessment of FENO as a potential noninvasive approach to examining asthma and track the effectiveness of anti-inflammatory medication was rapidly motivated by the study of exhaled nitric oxide measurement.

Before FENO could be utilized as a clinical tool, a number of problems needed to be solved. In particular, it was necessary to standardize the techniques and tools used to measure FENO. To assess the impact of influencing variables and cutoff points of FENO values, large population studies were required[14]. The majority of these problems have either been resolved or are actively being researched allowing FENO measurement to move from the domain of research into the clinical setting. The test's non-invasiveness, repeatability, and general simplicity of use in patients with substantial airflow obstruction, when other procedures are challenging to execute, are all advantages of FENO[14]. FENO offers a novel perspective to the conventional clinical tools including the history, physical examination, and lung function testing by supplying data on airway inflammation.

The achievement and maintenance of asthma control are the cornerstones of asthma therapy; however, the diagnostic abilities of the Asthma Control Test (ACT) and Asthma Control Questionnaire (ACQ) have not been extensively assessed. In clinical practice, the ACT is preferred over the ACQ, and the ACQ needs more cross-validation. Additionally, the ACT and ACQ are useless for evaluating uncontrolled asthma[17]. According to a significant recommendation of the National Review of Asthma Deaths report, patients should have a systematic annual assessment that evaluates asthma control[5]. It is recommended that asthma control be assessed at each evaluation by using a validated questionnaire, for example, the Asthma Control Test (ACT) in adults and in children older

than 5, along with spirometry or peak forced expiratory variability measurement[18].

Experts developed the Asthma Control Test (ACT), which provides rating in numbers to evaluate asthma control. The ACT has 5 questions on how frequently patients have experienced asthma symptoms and whether patient have taken relief medicine in the preceding 4 weeks[19]. The ACT measures the frequency of breathlessness, night time or early awakenings, the need for the overall management of asthma, recovery medication, and productivity loss. Higher scores indicate better asthma control. With a possible total score that ranges from 5 to 25, every question is responded to on a 5-point scale. Asthma that is "not well controlled" is indicated by a score under 20, whereas asthma that is "well controlled" is indicated by a score over 20[19]. A clinician should consider modifying the present treatment plan or continuing it when the readings fall between 20 and 25.

More recent research has shown more encouraging findings regarding the use of FeNO in monitoring asthma[3]. It is necessary to develop and implement interpretative techniques for the various potential uses and applications for the assessment of asthma control in patients by FENO and ACT.

RATIONALE OF THE STUDY

Even though research on FeNO and its connection to inflammatory responses has made significant progress, its ability to forecast how asthma will be managed is still under discussion. FeNO can be used as a marker for steroid compliance as well as a measure of the severity and management of asthma over time because it is a Th2-mediated respiratory inflammation marker. As per deAbreu et al, When evaluating the management of asthma, the FeNO level may be helpful. The goal of this study was to ascertain if the FeNO test either alone or in conjunction with the ACT score can accurately reflect asthma management[20].

SIGNIFICANCE OF THE STUDY

In spite of the utilization of inhaled corticosteroids, NICE's latest recommendation advocates that when someone has symptoms of asthma, FeNO measurement might be used to help their treatment1. ACT and FeNO are currently being examined to see if they rank among the most frequently used metrics for evaluating asthma management effectiveness. Since FeNO can identify patients whose asthma would not improve with increased corticosteroid therapy due to low eosinophilic inflammation, asthma treatment can be considerably improved21. The results of the study could therefore assist physicians in selecting the most effective asthma management strategies.

HYPOTHESIS

FeNO is a helpful tool that can be utilised in the setting of an outpatient clinic to assist doctors in making better treatment decisions for asthmatic patients.

OBJECTIVES

- To determine whether FeNO and ACT can objectively assess the control of asthma in adult patients
- To analyse the clinical implications and characteristics of FeNO measurement in asthmatics and assess whether the mean or variations in FeNO levels during the control period are related to ACT values.
- To identify any potential relationships between FeNO and both the ACT score and the spirometry data of patients.
- To determine their use in reducing the dose of inhaled steroids.

Materials and Method

The study will employ a qualitative research methodology based on an analysis of previously published materials in light of the aims, objectives, and questions of the study. Through qualitative research, a challenging problem can be addressed from the viewpoint of the real world in a full, multifaceted, in-depth manner[22].

It will be possible to find and incorporate high-quality medical studies from which evidence-based medicine can be applied by conducting a literature review on the topic at hand. A thorough study of the literature is crucial in this area of research because it enables an in-depth analysis of pertinent randomized controlled trials (RCTs) and experimental trials, which in turn enables the formulation of broad deductions about the efficacy of treatments.

The study specifically used a "systematic literature review (SLR)" to compile data on the FENO test and ACT to treat adult asthma.

DATA EXTRACTION

In order to find published literature of asthma control in adult patients by fractional exhaled nitric oxide (FeNO) and Asthma Control Test (ACT) during the course of the previous 12 years, a thorough online systematic literature search technique was designed (2010-2022). Fractionated exhaled nitric oxide (FeNO) as well as test for Asthma Control (ACT) were among the specific keywords used.

STUDY SELECTION

This research was an observational, retrospective investigation. Between 2010 and 2022, the data was selected and extracted from the previous research papers. In order to get the most comprehensive and reliable data for the study topic, scholarly, reputable, and authentic literature was searched. Google Scholar, PubMed, and Science Direct resources were utilized.

Results were filtered to only include reviews that reported on FeNO and ACT assessments of asthma control in adult patients. The scope of the literature search was restricted to English-language studies on asthma control evaluation. The reference manager stores each and every one of the obtained references. In order to filter the findings based on the inclusion and exclusion criteria, the abstracts and, when necessary, the complete texts of every retrieved literature were examined. Patients were not excluded from the research based on gender, nationality, or any other demographic factor. The papers were evaluated in accordance with the listed inclusion-exclusion criteria in the first stage of the evaluation (titles and abstracts), and the complete text was examined in the second stage. A publication was examined in the second (full text) step when insufficient data was identified to eliminate it in the first stage. This search query result was a total of 18 studies that met our inclusion criteria and were selected and reviewed.

INCLUSION AND EXCLUSION CRITERIA

International criteria were followed in the diagnosis of asthma. All studies used in the SLR are written in English for the sake of clarity. To broaden the scope of research, the SLR includes publications published after the year 2011. All relevant publications from reputable journals were analysed. Moreover, papers including adult asthma patients and the terms asthma, FENO, and ACT have been included. Studies that did not fulfil the inclusion criteria were omitted from the search and analysis. The initial screening of the papers has been performed using PRISMA (The flow diagram depicts the flow of information through the different phases of a systematic review).

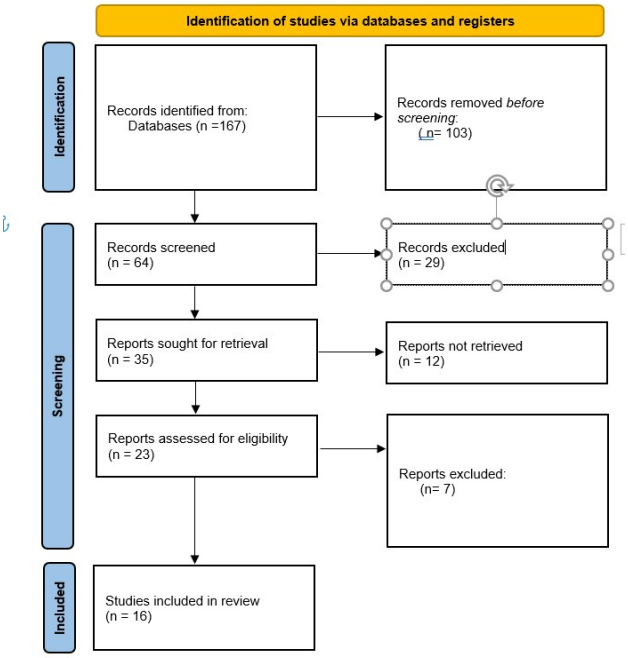

Figure 1: PRISMA

DATA MANAGEMENT

The clinical outcomes of three variables (ACT score, FeNO value, and FEV1) in patients with asthma were investigated during the monitoring period. Exacerbations of asthma and yearly changes in FEV1 during the follow-up period were the researched clinical outcomes. Rates per person annually were used to calculate the total number of asthma flare-ups throughout the control period. The term "asthma exacerbation" refers to the severity of asthma symptoms that occasionally require the use of systemic corticosteroids. A chemo-luminescence analyzer was used to test the FeNO level in the literature under evaluation. FeNO value was expressed in parts per billion (ppb).

In researched articles, calculated asthma control values in adult patients by Fractional Exhaled Nitric oxide (FeNO) and asthma Control Test (ACT) for qualitative factors were presented as percentages. For non-parametric data, constantly comparing variables were expressed as median and minimum-maximum values, and for

parametric data, as means and standard deviations (SD). Quantities and percentages are used to represent ordinal and nominal variables.

Results

The purpose of this literature study was to thoroughly examine the published literature on the topic of the Asthma Control Test and Fractional Exhaled Nitric Oxide (FeNO) Assessment of Asthma Control in Adult Patients (ACT). The examined population, key findings, and most importantly the asthma control strategies discussed in the literature found through an electronic search will all be covered in this chapter.

All age groups are affected by this major worldwide health issue, asthma. With 5.4 million individuals, including 1.1 million children, receiving treatment for asthma in the UK, the prevalence is significant. With 1370 asthma deaths in the UK in 2016, when compared to other high-income countries, the UK has the third-highest rate of deaths due to asthma.

This section presents a review of the selected studies. Basically, this section provides pieces of evidence from literature related to FeNO and ACT.

Overview of the selected studies:

Author	Study Title	Methodology	Results and Findings
Butler and Heaney[23]	"Fractional exhaled nitric oxide and asthma treatment adherence."	Qualitative	People who have Type-2 asthma who have high levels of biomarkers should be monitored for "inhaled corticosteroid adherence and FeNO response" in order to prevent the unnecessary advancement to biologic therapy. If an optimised FeNO is created, following clinical examinations may give light on underlying non-adherence.
Kavitha et al., 2017[24]	"Fractional exhaled nitric oxide is a useful adjunctive modality for monitoring bronchial asthma."	Participants were steroid-naive, ex-smokers with asthma who were monitored for 6-8 weeks while receiving conventional care. "FeNO, PEFR variability, FEV1, bronchodilator reversibility (BDR), and the Asthma Control Test (ACT)" score were all assessed at the beginning and end of therapy of 6-8 weeks.	FeNO may be useful as a non-invasive alternative for measuring asthma control before and after corticosteroid therapy. However, its below-average precision and sensitivity may limit its utility as a single surveillance technique at the point of care.
Kostikas et al., 2011[25]	"Exhaled NO and exhaled breath condensate pH in the evaluation of asthma control."	Two hundred seventy-four consecutive individuals had their "FeNO and EBC pH" tested after being exposed to Argon gas. According to GINA recommendations, two asthma experts examined asthma control using the "Asthma Control Test (ACT) and the Asthma Control Questionnaire (ACQ)".	Patients with poorly managed asthma may be identified by elevated levels of FeNO and pH in the EBC. However, they may only work for a subset of patients with asthma and their effectiveness was inadequate to that of clinical judgement.

Nguyen et al [26]	"The Asthma Control Test (ACT) as an alternative tool to Global Initiative for Asthma (GINA) guideline criteria for assessing asthma control in Vietnamese outpatients"	In order to evaluate the ACT and GINA classifications for asthma control, a cross-sectional study was conducted in 323 of 360 invited adult patients with asthma in Ho Chi Minh City.	The accuracy of the ACT with relation to concordance with the GINA categorisation was constant across both genders, although fewer in younger adults or adolescents. The ACT score was substantially linked with the percentage projected forced expiratory volume in 1 second ($r=0.35$, $p<0.001$) and percentage anticipated maximum expiratory flow ($r=0.26$, $p<0.001$). ACT has been found to be beneficial in diagnosing outpatients with uncontrollable or partially managed asthma according to the GINA criteria.
Bora et al[27]	"Does asthma control as assessed by the asthma control test reflect airway inflammation?"	Patients with asthma who performed the "Asthma Control Test (ACT), pulmonary function testing, and methacholine bronchial provocation test (MBPT)".	Even though the researchers found no correlations between ACT scores and the airway inflammation parameters they measured, the dramatic drop in the proportion of "patients with MBPT positivity and FeNO > 20 ppb" at follow-up may point to the significance of the control technique in the treatment of asthma.
Neelamegan et al[28]	"Clinical Utility of Fractional exhaled Nitric Oxide (FeNO) as a Biomarker to Predict Severity of Disease and Response to Inhaled Corticosteroid (ICS) in Asthma Patients."	"Inhaled corticosteroid treatment" for 8 weeks in individuals with asthma. At the beginning and the end of the study, a portable spirometer and a "chemiluminescence-based" exhaled breath analyser were used to quantify PFT and FeNO, respectively.	All three groups of asthmatics with mild, moderate, and moderately severe symptoms saw a significant reduction in mean FeNO levels after ICS treatment compared to similar baseline FeNO levels. As with the mean levels of FeNO, which were found to be significantly lower. It has been determined that there was no statistically significant difference between the groups in terms of asthma severity or ICS responders based on their baseline FeNO levels, as stated above. Decreases in FeNO levels on ICS treatment, however, support its clinical utility in monitoring ongoing airway inflammation and recognising response rate of intervention, despite the fact that the present study does not assist the inferential connection of baseline FeNO levels to symptom severity and prospective ICS reactions.

Kriti et al[29]	"Comparison of fractional exhaled nitric oxide, spirometry, and Asthma Control Test, in predicting asthma exacerbations: A prospective cohort study."	Cohort study with a future focus. The "Asthma Control Test (ACT) questionnaire" was used to measure the degree of asthma management. "FeNO, spirometry, and ACT" were all evaluated using the Mann-Whitney test to determine their predictive value, and the strength of their association was determined using "Spearman's correlation coefficient".	According to the results, FEV1% and ACT score can foretell asthma exacerbations, however FeNO cannot. ACT scores were inversely associated with FeNO concentrations. Inhaled corticosteroids reduced FeNO levels.

Petsky et al reviewed 1653 publications related to asthma and ACT, of them, 69 studies discovered a connection between rising ACT scores and improved outcomes[10]. Substantial confirmations were found for correlations concerning ACT score and use of relief medicine, exacerbations, work and efficiency. Significant evidence was found for relationships between ACT score and ACQ score, lung function, and asthma-related issues. Findings from the review supports the usage of the ACT in clinical research settings and imply that it is a suitable indicator of the overall burden of asthma[10].

Gill et al studied the association between ACT scores and FENO levels was calculated using a spearman correlation. The participants' average age was 41 years (4–93 years)[5]. Between ACT and FeNO, there was no statistically significant connection (r = 0.195, p = 0.120). The ACT score was 20, and the median FeNO was 26 ppb (range 8-279 ppb) (range 5 to 25 points). Additionally, FeNO causes medication changes more frequently than ACT, 66% versus 42% (p = 0.005)[5].

Karrasch et al conducted a study of diagnostic meta-analysis, included 26 studies with 4518 individuals[30]. The meta-overall analysis's sensitivity was 0.65 that is 95% confidence interval, overall specificity was 0.82, diagnostic OR was 9.23, and the areas under the curve was 0.80 or ranges from 0.77 to 0.85. The meta-overall analysis's sensitivity was 95% CI. Higher cut-off readings were linked to higher specificity in meta-regression analyses, increasing by 1.46 every 10-ppb increase, but there was no link to sensitivity. Within the various FENO devices, sensitivity ranged widely. When used to diagnose asthma, FENO seems to have a fair degree of accuracy[30].

Calhoun et al evaluated a substantial relationship was discovered for FeNO content at diagnosis and the asthma treatment[31]. The relevance of the average FeNO concentration and the percent difference of FeNO ranks in measurements collected during the course of treating asthma were assessed in the secondary evaluation. There were no significant positive correlations between FeNO rates as well as other constraints, such as Expiratory volume in a second or an ACT score, as well as a percentage adjustment to standards values during the first 5 dimensions while undergoing asthma therapy. The final evaluation looked at the relationship between the three measures from the monitoring period and the clinical outcomes of asthma patients. Although there was a very significant inverse association between the mean ACT score and percent predicted FEV1 and infrequent usage systemic corticosteroids, there was a substantial negative link between the FeNO level and yearly basis variation in FEV1 in asthmatics who were surveyed up for longer than two years. A substantial negative association between the ACT mean score and percent estimated FEV1 was found, along with the infrequent use of systemic corticosteroids[31].

Out of 175 studies were analysed by Petsky et al, 43 studies found that FeNO results increased the likelihood of successfully diagnosing asthma by 5.85 to 16.95 fold in both adults (>18) and children ages 5 to 18 years[11]. FeNO testing had sensitivities of 0.79, 0.64, 0.53, and 0.41, and specificities of 0.72, 0.81, 0.84, and 0.94 with FeNO cutoffs of 40 ppb, respectively. Depending on the FeNO cutoff, a positive FeNO test result

increased the probability of having asthma by 2.80 to 7.00 times[10]. Children, nonsmokers, and asthmatics who had never used steroids had slightly higher diagnostic accuracy than the general population. Data from 58 studies revealed that FeNO levels in both adults and children (aged 5 to 18) were weakly correlated with asthma management and the risk of current and past exacerbations. In people with atopy, elevated FeNO levels were probably more predictive of the probability of an exacerbation. FeNO levels were difficult to reproduce and did not correspond with the severity of acute asthma exacerbations in adults or children. FeNO levels were inversely correlated with compliance to inhaled corticosteroids in children and adolescents (age ranges 5 to 18). Data from 14 randomized controlled trials revealed that FeNO monitoring in asthma management algorithms reduced the likelihood of exacerbations but had no effect on the quality of life or other outcomes, such as hospitalization. Patients who were more likely to respond to inhaled corticosteroids may be identified by FeNO testing. In patients undergoing ICS reduction or removal, FeNO testing identified exacerbations in advance. According to data from nine research, wheezing and FeNO levels in children between the ages of 0 and 4 were connected with the Asthma Predictive Index, but there was insufficient data to say whether or not FeNO values at that age may accurately predict future diagnosis of asthma[11].

At King Saud University in Riyadh of Saudi Arabia, Habib et al recruited 59 adult asthmatics, 53 of whom completed the study between July 2011 and June 2012[32]. Those with an ACT score of 20 or higher had substantially higher FENO values ranges from 65.5–35.4 than patients with an ACT score of 20 or lower that is 27.4–10.5, p0.001. FENO levels with ACT scores have a negative correlation, however there is no connection between FENO and lung function. A continuing inflammatory state is seen in patients with inadequate asthma management, according to a substantial correlation between ACT score and FENO levels[32].

Sato et al studied 370 asthmatics who underwent FeNO measurement, ACT, as well as spirometry was performed for a clinical evaluation during the research period[33]. In the controlled periods, the mean (SD) main improvement in FeNO levels was 62.2 ppb. FEV1 Statistical significance was defined as a p value 0.05. Researchers looked at the linear association between ACT scores and FeNO concentrations. P values of 0.05 or less were regarded as significant. FeNO levels at the time of diagnosis and the main improvement in FeNO throughout the monitoring period were found to be strongly positively correlated (P <.001)[33].

Llano et al analyzed the reliability of benchmark exhaled nitric oxide fraction (FeNO) to identify people with difficult-to-treat asthma[34]. 102 patients in a succession with inadequate asthma control got gradual increases in the maximum fluticasone or salmeterol dosage for one month of treatment, the people who took oral corticosteroids for an additional month while remaining controllable. This method helped 53 patients (or 52%) acquire control. Increased respiration variability of 20% (71.1% against 49.1%; p50.04) and positive bronchodilator test (57.1% over 35.8%; p50.02). In contrast, individuals who continued to be uncontrolled experienced depression more frequently (18.4% vs. 43.4%; p50.01). For the detection of responsive asthmatics, a FeNO value of 30 ppb showed a sensitivity of 87.5% (95% CI 73.9-94.5%) and a specificity rate of 90.6% (95% CI). According to this research, FeNO can be used to identify asthma patients who are difficult to treat and may respond well to large doses of systemic corticosteroids[34].

As per Hanania et al[3] Clinicians from 337 US practises evaluated 7,901 asthma patients clinically and documented their treatment regimens both before and after testing FeNO. Only 56% of clinical assessments and FeNO measurements matched, with low inflammation patients matching FeNO more frequently (64%) than patients with significant inflammation (34%). Following FeNO measurement, 31% of patients had their treatment regimen changed, and 90% of patients had their inhaled corticosteroid prescriptions changed. Only 9% of patients with minimal inflammation had their inhaled corticosteroids terminated or reduced in dose, compared to 66% of patients with significant inflammation. Comparatively to an actual clinical evaluation of asthma alone, measurement of FeNO allowed doctors to evaluate underlying airway inflammation, which resulted in a major adjustment of their treatment strategies[3].

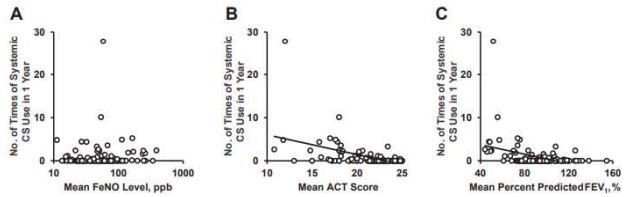

Figure 2: Illustrated the Control of asthma symptoms and case count with sporadic use of systemic corticosteroids (CSs).

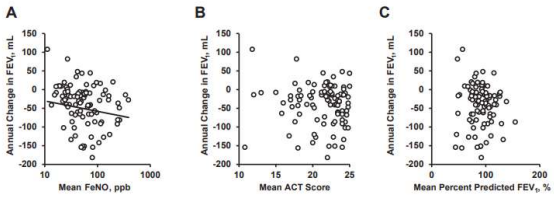

Figure 3: Showing the Forced expiratory volume in one second (FEV1) control variables and annual variations (N=99)

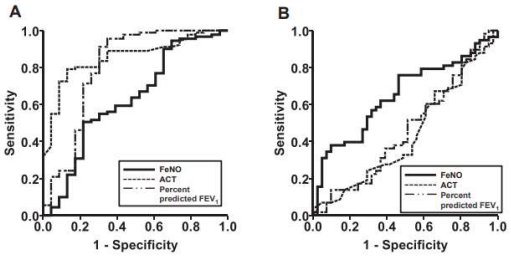

Figure 4 (a, b): Showing the Asthma Control Test (ACT) scores and fractional exhaled nitric oxide (FeNO) assessments of mean values using receiver operating characteristic (ROC) data.

The findings of the research project that was based on the aforementioned paper indicate that there is not yet sufficient evidence to draw the conclusion that FeNO and ACT might be the gold standard approaches for controlling asthma in patients. According to the findings of the research, using FeNO as a supplementary non-invasive method for assessing asthma control may be effective in both steroid-naive asthmatics and asthmatics who are being treated with steroids. However, because of its poor sensitivity and specificity, its use as a single monitoring tool at the point of care might not be as effective as it could be[24]. Comparatively, evaluating adherence and FeNO response to monitored inhaled corticosteroid treatment may prevent the needless progression to biologic therapy in asthmatic patients with Type-2 biomarker levels that are high. It is possible that in future clinical evaluations, an "optimized" FeNO will alert medical professionals to the possibility of underlying non-adherence23. Patients suffering from asthma who do not have their condition under good control may be recognised by elevated levels of eNOS[25]. The ACT is a reliable and straightforward diagnostic tool due to the fact that it does not include readings from complicated spirometry equipment. This has the potential to be an extremely helpful tool for the treatment of asthma in patients who are receiving their care outside of a hospital setting. There is a close connection between the score on the questionnaire and the modifications to treatment as well as the measurements of lung function.

The Asthma Control Test (ACT) is a brief and easy-to-understand questionnaire that patients are asked to fill out. This questionnaire has the potential to become an invaluable instrument for guiding changes in the management of asthma in clinical practice[26]. In addition, ACT is recommended in conjunction with tests of pulmonary function and/or measurements of eNO35. However, there was not a significant correlation between the scores on the ACT and the airway inflammatory measures that were evaluated by Bora et al[27]. The researchers who conducted this study found that patients who were given controls had lower levels of bronchial reactivity and FeNO as compared to controls. Following treatment, bronchial reactivity and levels of nitrous oxide (NO) were found to have significantly decreased, according to the study[27].

Discussion

Getting and keeping asthma under clinical control is the primary focus of asthma therapy. It can be challenging for a physician to decide the treatment to an asthma patient and in what dosage to give them of that medication. Inhaled corticosteroids, also known as ICSs, and other treatments improve lung function and asthma management, lessen symptoms experienced during the day and at night, and cut down on the number of times asthma attacks occur. The degree to which an individual responds to a specific dose also varies from person to person, and a significant number of individuals do not appear to react in any way to the medication that is being administered. Sputum induction for eosinophil testing is one of the established methods for better characterizing airway inflammation and advising corticosteroid responsiveness; however, it is not widely

available. Sputum induction is performed in order to test for the presence of eosinophils.

Non-adherence to inhaled corticosteroid therapy continues to be a major obstacle to effective asthma management and poses a risk of improper drug escalation, especially in severe cases of the disease, despite increased clinician awareness of this problem. This is especially true in cases where asthma symptoms are severe. Those individuals who have Type-2 mediated pathology have the ability to use fractional exhaled nitric oxide, also known as FeNO, as a method to monitor the efficacy of inhaled corticosteroid treatment. Numerous reviewed articles and recommendations strongly support its usage as an asthma biomarker. Additionally, there is evidence to support the cost-effectiveness of its usage in clinical settings for patients with uncontrolled asthma given its capacity to enhance the accuracy of the diagnosis of asthma and monitor therapy response[36]. According to the findings of the research conducted by Butler and Heaney, individuals who had elevated FeNO levels and uncontrolled asthma were more likely to experience an exacerbation if they did not follow to the treatment regimen that was prescribed to them23. A common contributor to elevated levels of FeNO is a lack of adherence to inhaled corticosteroid medication, whether this is done unintentionally or on design. If non-adherence is recognized, asthma control may be improved, and the expensive use of biologic medications may be minimized. Both of these outcomes would be favorable. According to the findings of this study, screening patients with Type-2 biomarker-high asthma for adherence and FeNO response to monitored inhaled corticosteroid treatment may be an effective way to reduce the proportion of patients who are mistakenly promoted to biologic therapy. Prior to further clinical studies, the creation of an "optimized" FeNO could serve as an early warning system for underlying non-adherence[23].

It is significant to note that the FeNO threshold values employed in each of the six studies under review which ranged from 20 to 45 parts per billion were different. It is challenging to compare the outcomes of trials with various strategies since the analytical value of FeNO for steroid response varies significantly depending on the cutoff value selected[36]. However, these studies collectively imply that FeNO alone cannot reliably predict the precise amount of inhaled corticosteroid needed in a specific patient. The best technique to establish if the current dose of inhaled corticosteroid is sufficient to manage airway inflammation is instead to utilize FeNO. Between people, considering the wide variation in FeNO levels, it is possible that baseline heterogeneity in mucosal nitric oxide synthase activity and the contribution of additional no eosinophilic variables to epithelial nitric oxide synthase activity are responsible[14].

According to the findings of Kavitha et al, the levels of FeNO increased in asthma patients as the airway obstruction became more severe. Because there were not enough participants in the study, the author was unable to determine what the optimal range of FeNO levels should be for categorizing the severity of asthma[24]. If something like this had occurred, we would now have the knowledge to understand that testing for FeNO can be helpful in determining the severity of a disease either as a surrogate or at the very least as an additional method. Few studies have been conducted on adults, despite the fact that there is evidence that increased FeNO levels are associated with more severe asthma in adolescents. It is not known whether or not FeNO can accurately measure asthma treatment at this point in time. It has been reported that several asthma monitoring markers have a weak but positive correlation with FeNO levels at baseline. Kostikas et al. discovered, in a study that included 274 participants that FeNO was able to differentiate between people whose asthma was poorly managed and those whose asthma was well-controlled[25]. They came to the conclusion that even though the level of FeNO in patients who received inadequate care was higher, it was still lower than the ACT score. Therefore, despite the fact that FeNO may be able to detect poor asthma control, it cannot take the place of clinical judgment and may only be beneficial in a subset of asthmatics.

It was shown that there was a significant relationship between the patients' FeNO levels and their FEV1, PEFR variability, and ACT scores at the beginning of the study[24]. However, after therapy, the strength of this association remained the same with ACT score by itself. These findings are comparable to those reported by Papakosta et al who discovered important correlations among FeNO and ACT score ($r = 0.211$, $P = 0.007$) at baseline but not during therapies with

steroids, and with Caminati et al, who discovered an excellent correlation between exhaled nitric oxide and ACT in 27 newly diagnosed asthmatics ($r = 0.7$, $P = 0.001$)[37,38]. Neither of these researchers found significant interrelationships among FeNO. On the other hand, an analysis of FeNO among two distinct ethnic groups and discovered that there was no association among ACT and FeNO across populations. Therefore, it is possible to draw the conclusion from the findings presented above that in steroid-naive asthmatics, the level of FeNO affects the intensity of symptoms, as well as airflow restriction, PEFR variability, and airway hyperresponsiveness. On the other hand, Bora et al set out to examine the correlation between ACT, pulmonary function, "methacholine bronchial provocation test (MBPT)" outcomes, nitric oxide (NO) levels, and eosinophilic induced sputum[27]. After making therapy adjustments in accordance with ACT, they also checked for changes in these variables. According to the research, there was no statistically significant correlation between the two groups, patients on control had reduced bronchial reactivity and decreased FeNO levels compared to controls. Moreover, it has been shown that both bronchial reactivity and FeNO levels significantly improve at the follow-up appointment[27]. In line with this a study evaluating bronchial hyperreactivity in asthmatic patients has shown that 86% of totally controlled patients had MBPT positivity and suggested that airway inflammation and bronchial hypersensitivity continue even in a totally controlled state[39]. There are studies that have shown poor asthma control in patients with MBPT positivity[40,41]. While in the study of Bora et al, the proportion of patients with positive MBPT showed a statistically significant decrease within three months of follow-up and treatment[27]. When the association between asthma control level and MBPT positivity was analyzed, MBPT positivity was observed in 62%, 56%, and 62% of the totally controlled, partially controlled, and uncontrolled patients at the baseline visit. At the follow up visit, these figures decreased to 30%, 54%, and 38%, respectively.

It is vital to perform routine assessment of the asthma severity in addition to utilising the various therapy modalities in order to keep asthma under control. The value of FENO is used to assess the severity of an asthmatic patient's illness, and this assessment in turn is used to estimate the required dosage of maintenance medicine. Patients who have a high FENO score typically have a severe form of asthma, which requires more advanced treatment in order to achieve optimal control of airway inflammation and a managed asthma status. Patients who have a high FENO score also tend to have a longer hospitalisation time. However, the intensity of symptoms and the degree to which an individual's airways are irritated can vary greatly from person to person. These disparities can be attributed to the impact of ICS as well as the demographic variety that exists. As a result of its non-invasive nature, ease of administration, sensitivity, and repeatability, FENO has emerged as a candidate for use as a biomarker in the evaluation of airway inflammation. Even in the absence of significant symptoms, the treatment of asthma symptoms and the medication that is being used must depend on the type of airway inflammation and the quantification of inflammatory responses. This is necessary in order to prevent the worsening of asthma and the induction of exacerbations. An integrated approach is required in order to diagnose asthma patients accurately and to continue to monitor their condition. The inclusion of clinical examination, evaluation of functional status, and airway inflammatory biomarkers are all necessary components of this technique. FENO is an alternative that can be considered in order to monitor the severity of asthma, follow up on care, and improve the process of controlling asthma symptoms.

When compared to other objective tests, such as lung function, FeNO, and bronchial challenge, asthma specialists discovered that the ACT, with a cut-off value of less than 20, was significantly connected with the increase in the dosage of asthma medications. This was the case even though the ACT measured a different variable. Ko et al released their findings to provide evidence for this finding in their study. When compared to the use of other quantitative measures of pulmonary function, the Asthma Control Test (ACT) did not perform significantly better on its own in predicting the change in asthma medication[42]. This was the case irrespective of whether or not any other indicators were taken into consideration.

FeNO surveillance has allowed medical personnel to discover baseline inflammatory responses, which has led to similar results as clinical assessment of asthma alone may lead to

significant changes in treatment regimens. Similar to how clinical assessment of asthma alone may lead to significant changes in treatment regimens[3].

Kriti et al, carried out a study to investigate the connection between these three tests and to compare and contrast the predictive ability of "FeNO, spirometry, and the asthma control test (ACT)." It was discovered that the FeNO readings had a predictive value for asthma exacerbations that was significantly lower than that of the ACT scores[29]. According to the findings of the research conducted by Kriti et al FeNO levels are not helpful for predicting asthma attacks. The outcome was consistent with what has been uncovered in the past[29]. It was discovered that FeNO was unsuccessful in predicting asthma exacerbations in children, whether it was used alone or in combination with symptom ratings. This was the case regardless of which approach was taken. FeNO may be able to predict future exacerbations even in the absence of a prior history of exacerbations, according to the findings of a prospective study that was conducted on 109 people who suffer from asthma over the course of three years. It has been established that FeNO, when combined with a positive "bronchodilator reversibility," can anticipate an asthmatic patient's loss of control.

According to the findings of a study that was carried out by Menzies and her colleagues, patients whose asthma was poorly treated had greater levels of FeNO[43]. The elevated levels of FeNO may indicate that the patient's asthma medication needs to be increased, or they may be the result of the patient not taking their meds as directed. Either way, the patient should see their doctor as soon as possible. In particular, research by Kriti et al found that there is a negative correlation between one's ACT score and the level of FeNO[29]. FeNO may be an indicator of poor treatment of symptoms, despite the fact that it cannot forecast exacerbations. This is despite the fact that FeNO cannot predict exacerbations.

According to Kriti et al's research, levels of FeNO were observed to rise with advancing age[29]. On the other hand, various patterns of drop in FeNO with age have been discovered by other researchers. Researchers conducted a few tests and found that as the subjects aged, their levels of FeNO increased. In a study carried out in Thailand, researchers found that levels of FeNO began to rise between the ages of 11 and 15, and those levels continued to rise until participants reached the age of 47 and beyond[44]. In addition to this, it was discovered that adult males have higher amounts of FeNO compared to adult females. Research carried out by Olin et al. uncovered the objective requirements for FeNO in individuals who did not smoke and were in good health[13]. The findings indicated that age and height were the most important determinants in determining FeNO, while gender was irrelevant to the process. An investigation was conducted to determine whether or not the proposal was successful in preventing asthma episodes and making the best use of corticosteroids. According to the findings, an asthma treatment plan that is based on FeNO measurement does not significantly reduce the number of asthma exacerbations or the total quantity of inhaled corticosteroid medication that is required over the course of an entire year in comparison to the recommendations that are currently in place for asthma treatment.

According to the findings of Neelamegan et al, after ICS medication, there was a substantial difference in the mean FeNO levels across the mild, moderate, and moderately severe asthmatic groups[28]. This was the case even among patients whose baseline FeNO levels were the same. Despite the fact that the findings of the study conducted by Neelamegan et al, did not support a predictive association between baseline FeNO levels and asthma severity and ICS response, the decreases in FeNO levels on ICS treatment lent credence to the clinical utility of the biomarker in tracking ongoing airway inflammation and gauging the effectiveness of treatment[28]. If it is tracked in prospective studies with a larger sample size and longer follow-up time (>8 weeks), then a better understanding of the predictive association of FeNO as a diagnostic biomarker of both sickness severity and ICS response can be achieved. In clinical practice and asthma diagnosis, recommendations to use FeNO have been drawn from systematic reviews, guidelines from the Global Initiative for Asthma (GINA), and guidelines from the American Thoracic Society (ATS); however, these recommendations are not robust due to heterogeneity in study reports, and more research is required. In the future, clinical practice may stand to gain from routinely

measuring FeNO in addition to other parameters in order to determine how to best treat asthma. When the long-term consequences of ICS treatment are considered, as well as the frequency of exacerbations across all age groups, it is clear that additional research on this particular "asthma phenotype" is required.

LIMITATIONS OF STUDY

Some restrictions applied to this systematic study. At one point in the current investigation, the variable factors for predicting potential exacerbations were found. Even when their asthma has been controlled, asthmatics are constantly susceptible to exacerbations during acute respiratory infections. Future research must therefore focus on evaluating asthma controls at various points.

Conclusion

Using FeNO as a supplementary non-invasive method for assessing asthma control may be effective in both steroid-naive asthmatics and those who are being treated with steroids. Because of its poor sensitivity and specificity, its use as a single monitoring tool at the point of care might not be as effective as it could be. Standardized cut-off values may not be an adequate general marker for all asthma patients for continued asthma treatment using FeNO levels. Evaluating adherence and FeNO response to monitored inhaled corticosteroid treatment may prevent the needless progression to biologic therapy in asthmatic patients with high Type-2 biomarker levels. The Asthma Control Test (ACT) has the potential to become an invaluable instrument for guiding changes in the management of asthma in clinical practice. There is a close connection between the ACT score and the modifications to treatment as well as the measurements of lung function.

Several asthma monitoring markers have been reported to have a weak but positive correlation with FeNO levels at baseline. FeNO may be able to detect poor asthma control; however, it cannot substitute for clinical judgment and may only be beneficial in a subset of asthmatics. There can be a wide range of differences between people in terms of the severity of their symptoms and the degree to which their airways are irritated. Patients who have a high FENO score almost always have a severe form of asthma, which calls for more intensive medical care. In order to diagnose patients with asthma correctly and to continue to monitor their condition, an integrated approach is required. It was found that using FeNO alone or in combination with symptom ratings did not improve its ability to predict asthma exacerbations.

The researchers discovered that the levels of FeNO in the subjects increased as they got older. When determining FeNO, age, and height were the most important factors to consider; however, gender played no role in the calculation in any way. It is possible to use FeNO as a diagnostic biomarker of both the severity of the illness and the response to ICS, it accepts our study hypothesis. It is abundantly clear that additional research on this specific "asthma phenotype" is essential in light of the fact that the long-term effects of ICS treatment, in addition to the frequency of exacerbations across all age groups, should be taken into consideration.

FUTURE RECOMMENDATIONS

Symptom questionnaires, significant airflow obstruction and severe asthma exacerbations are among the factors that have been shown to be useful in predicting future asthma episodes. Non-invasive markers for predicting asthma exacerbations include objective measures of ACT and the fraction of exhaled nitric oxide (FENO). Additionally, stratifying the risk for asthma exacerbations can be done by combining the FENO and percentage of projected forced expiratory volume in one second (FEV1). It has not yet been established if a combination of these characteristics is a reliable index to anticipate asthmatic exacerbations, despite the fact that standard measurements of lung function are an essential predictor of severity but are insufficient as an index of asthma management. It is crucial to confirm whether extra clinical information can make forecasts more accurate.

It is essential to conduct more prospective research to confirm findings in a sizable asthmatic population. Further investigation is also needed to determine the mechanisms underlying the rise in FeNO levels with the deterioration of lung function in asthmatics.

Clinical data can be used to correctly predict asthmatic patients' exacerbations. Examining in-depth clinical data, such as airflow restrictions, may offer crucial additional markers of the exacerbation risks. In comparison to a single

evaluation of each, it has been shown that the combination of the Asthma Control Test and respiratory symptoms will be a more effective tool for predicting future asthma exacerbations. Future research is required to assess the patient and airway function-based management of asthma by determining the therapeutic role of reduced dosages of inhaled corticosteroids or other anti-inflammatory medications in maintaining asthma control without asthma exacerbations.

The use of FENO is recommended in the diagnosis of eosinophilic airway inflammation. It is advised to use FENO to assess if a person with chronic respiratory symptoms who may have airway inflammation will likely respond to steroids. Also recommended that FENO could be utilized to support an asthma diagnosis when objective verification is required. Researchers advise using low FENO levels of fewer than 25 ppb (or 20 ppb in youngsters) to suggest that eosinophilic inflammation and corticosteroid response are less likely.

Future suggestions recommend utilizing the following thresholds to assess if there has been a meaningful increase in FENO, greater than 20% for values over 50 parts per billion or more than 10 parts per billion for values below 50 ppb from one consultation to the next.

Even though these recommendations for FENO measurement interpretation will increase their clinical utility, researchers still need to look into the best ways to interpret FENO results in various clinical scenarios. Understanding the function of FENO in assessing therapeutic response would benefit greatly from its inclusion as an endpoint in clinical trials. In addition, the National Health and Nutrition Examination Survey and other sizable population-based studies might yield more information on standard values if FENO measurements were used. Thus, in order to reflect new advancements in this quickly changing subject, the standards offered here will need to be modified from time to time.

FeNO is a trustworthy, non-invasive, and repeatable test for identifying asthmatic patients' airway inflammation that correlates with disease activity. In controlling the symptoms of asthma treatment is the primary objective. Fractional exhaled nitric oxide (FeNO) levels, and asthma control test (ACT) scores can all be used to evaluate an asthmatic's symptom control and severity.

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