Clinical correlation between exhaled nitric oxide measurements in patients of asthma with their Asthma Control Questionnaire Scores

Tinguria Nikita[1], Tayade Balkrishna[2]

Abstract:

Fractional exhaled nitric oxide (FENO) is a specific index for the measurement of airway inflammation and Asthma Control Questionnaire score (ACQ score) is a nonspecific index of asthma control and symptoms for a variety of obstructive diseases. In this study, no simple linear correlation was found between the two. Long term monitoring of management and control of atopic allergic bronchial asthma in a larger sample size and correlating it with adequate ICS therapy and ongoing treatment, can help to closely evaluate the link between ACQ and FENO levels. Only selected atopic-allergic bronchial asthma patients should be considered.

Keywords: Fractional Exhaled Nitric Oxide (FENO), Asthma Control Questionnaire score (ACQ), Airway inflammation, Asthma control, Atopic-allergic asthma.

[1]Intern, [2]Professor and Head, Department of Pulmonary Medicine, NKPSIMS&RC, Digdoh Hills, Hingna Road, Nagpur-440019. nikita.tinguria12@gmail.com

Introduction:

Asthma is a type of Obstructive Pulmonary disease which involves chronic airway inflammation and an increase in airway hyper responsiveness. Bronchial Asthma can be defined as a complex syndrome having the characteristic symptoms of wheezing, coughing, chest pain, dyspnoea, along with airway inflammation, decreased airway caliber, impaired lung function, airway hyper responsiveness and airway remodeling (1).

Bronchial Asthma can be of two types: Extrinsic (allergic, atopic asthma) and Intrinsic (non-atopic asthma).

Extrinsic asthma:

It is the more common form of asthma. It is partially reversible with medication and is always triggered by allergens such as dust, mites, pollens, mold etc. The body's immune system exerts a protective reaction to these allergens and produces antibodies. This results in symptoms such as hay fever, rhinitis, and asthma. These allergens induce a complex reaction in which large amounts of mucus is produced which causes the lung airways to become obstructed, inflamed and swollen.Allergic asthma occurs more commonly in children and in individuals with a family history of allergens. Symptoms in allergic asthma can be controlled by avoiding allergen exposure, as well as use of bronchodilators and antihistamines.

Intrinsic asthma:

Intrinsic asthma on the other hand, is not associated with an allergic reaction. It is triggered by factors such as stress, anxiety, extremes of emotional feelings like laughing or crying or exercise, cold dry air, hyperventilation etc. These factors stimulate a nerve response in the airway passage. Non-allergic asthma is seen more commonly in adults, female patients, and with Forced Expiratory Volume in 1 Second (FEV1) below 80%. Interestingly, there is a more frequent association with sinus polyposis.

Non allergic asthma can be objectively distinguished from allergic asthma based on negative skin tests, whereas positive skin tests show tendencies to produce immunoglobulin E(IgE) antibodies (2). Intrinsic asthma is also more difficult to treat as the causative agent is unknown.Normally, Nitric Oxide in exhaled air originates from the respiratory epithelium where it is produced by inducible NO synthase (INOS). Inducible NO synthase is regulated by signal transducer and activator of transcription (STAT-1) under the influence of interferon - gamma. In asthmatics, the endogenous fractional exhaled nitric oxide (FENO) levels get elevated. Nitric oxide therefore plays an intrinsic part of inflammation. The INOS expression is up regulated by interleukin -4 and interleukin - 13. This occurs through the activation of STAT-6 in the bronchial epithelium. FENO is therefore a critical and a sensitive marker as it responds rapidly to inflammation after allergen exposure. It also helps predict the response to anti-inflammatory therapy and to monitor the anti-inflammatory effect (3).

The assessment of FENO gives an accurate diagnosis of airway inflammation in about 80% patients. FENO greater than 50 parts per billion (ppb) (greater than 35 ppb) indicates than eosinophilic inflammation and response to corticosteroids is likely (4). FENO levels can increase even before the onset of symptoms and is therefore helpful in predicting asthma.

The most important element of Asthma management is Asthma control. The Global Initiative for Asthma (GINA) guidelines suggest that asthma control can be divided into three levels: well controlled, partly controlled, and uncontrolled. This can be assessed by the Asthma Control Questionnaire Score. The ACQ (validated as per Elizabeth

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Juniper) was used to judge their level of control based on symptoms they had at the time of correlation. It contains 7 questions and the patients were asked to recall their asthma symptoms in the past week which includes day and night symptoms (sleep patterns), limitation of activities, shortness of breath and wheeze along with FEV1 predicted and daily bronchodilator use. The patients were then asked to respond to their asthma symptoms based on a 7 point scale (0 - no improvement, 6 - maximum improvement). The final ACQ score was therefore the mean score of all the 7 questions, ranging between 0 and 6. The normal control subject had a score of less than 1.0 meaning well controlled asthma. Any patient with an ACQ above 1.0 did not have a well-controlled asthma. Not much efforts have been made to correlate the relation between exhaled Nitric Oxide (NO) measurement in asthmatic patients with their asthma control Questionnaire Score and hence this study.

Material and Methods:

The present study was carried out at NKP Salve Institute of Medical Sciences and Research Center, Nagpur in the Chest and TB OPD. The duration of the study was two months. Permission from the Institutional Ethics Committee was taken for this research.The sample size calculated was 42 patients. Control subjects were having normal FeNO between 5-25ppb, and an ACQ of less than 1.

The Inclusion/Exclusion criterion was as follows:
Inclusion criteria:
Known cases of allergic bronchial asthma with demonstrable reversibility in FEV1 as per the GINA guidelines (namely well controlled, partially controlled and uncontrolled).

Exclusion Criteria:

Smokers,chronic obstructive pulmonary disease (COPD), airway viral infection, allergic rhinitis (concomitant), nitrate-rich diet, spirometric maneuvers, exercise, alcohol consumption, bronchoconstriction, ciliary dyskinesia, hypertension, cystic fibrosis cases were excluded from the study.

The materials required to carry out the research included the following:
1. Patients of both Extrinsic and Intrinsic type
2. Asthma Control Questionnaire
3. Aerocrine analyser "NIOX MIO" to measure FENO levels
4. Spiro meter to measure FEV1 (Forced Expiratory Volume

1) The participants were administered the ACQ and the scores were tallied. The FENO measurements were followed after this. FENO was measured using a chemiluminescence analyzer (NIOX-system; Aerocrine AB; Solna, Sweden) to measure exhaled NO during a slow, single exhalation against an oral pressure of 5cm $H_2O.20$. The procedure was

performed repeatedly to obtain two or three reproducible values. Normal FENO values range between 5-25 ppb. Any FENO value above 25 ppb indicates eosinophilic airway inflammation.

This was then followed by spirometry required for the ACQ scores. It was performed using a dry wedge spirometer to provide estimates of forced vital capacity (FVC) and FEV1. Patients who were prescribed corticosteroids had to undergo another FENO measurement before and during the anti-inflammatory therapy just to check whether the patients were responding well to the therapy.

The scores obtained from the ACQ and the FENO values were then evaluated to consult if a clinical correlation existed between the two, to reflect their level of asthma control.The statistical analysis was carried out using the Chi Square test. The Chi Square Test is used to test the significance of difference between two proportions.

Results:

Table 1 and 2 depict the FeNO value and ACQ scores in males and females.

Table 1: FENO vs ACQ scores in Females

AGE	FENO value	ACQ score
41	6	2.43
18	6	1.43
26	8	1.9
28	6	1.43
52	14	3
47	16	1
8	12	2.3
60	17	1
59	10	2
28	9	2.5
27	34	1.14
60	20	1.3
45	29	3.14
60	11	1.5
46	33	3
60	24	1.1
43	90	2
30	131	1.14
62	10	2.15
60	11	1.29
31	30	2.4
20	110	2.4
40	18	2.14
55	5	1.9
47	7	2.7
56	6	3
30	13	2.45

Table 2: FENO vs. ACQ scores in Males

Age	FeNO value	ACQ score
45	147	1.1
19	36	1.1
51	30	1.4
47	126	2.9
60	7	2.9
17	5	2.4
45	39	1.4
51	28	1.7
35	9	3.2
33	12	1.5
55	5	1.32
42	18	2.2
59	30	1.32
40	55	3.5

As from Fig. 1, there is no linear, significant clinical correlation between FENO measurements and Asthma Control Questionnaire scores i.e. the MEAN FeNO Value (ppb) = 30 ppb. The MEAN ACQ Value = 2.01
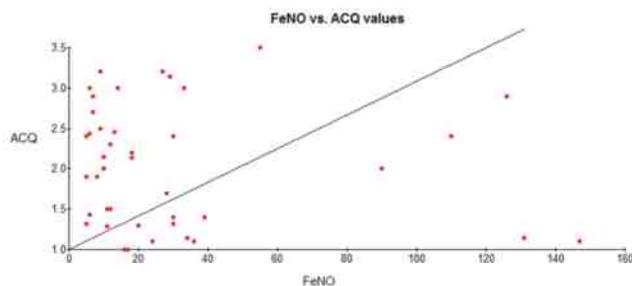
Fig. 1- Scatter diagram showing relation between FENO and ACQ values in 41 patients

The ability of FENO measurements to reflect the asthma control was investigated. The asthma control questionnaire scores and FENO measurements were recorded once in 41 asthma patients between 17-60 years of age. 16 patients with high FeNO measurements of more than 25ppb, had normal or mild ACQ scores. This shows that the extent of bronchial airway inflammation is not proportionate with asthma control and symptoms. The data are presented as mean, n(%), FEV1 : Forced expiratory volume in one second; % predicted Chi-Square test as applied to asthma patients showed

	Normal	Abnormal	Total	Abnormal Rate
FENO	26	15	41	36.5%
ACQ	6	35	41	85.3%
Total	32	50	82	

As in Table 3, the probability of 5% was adopted as standard. Since the chi square value of 20.69 is greater than the probability of 0.05 with x square of 3.84, we conclude that the null hypothesis is rejected and that FeNO and ACQ are not equal markers of asthma and that one is superior to the other (Table 4).

Table 3: Clinical Characteristics of 41 selected asthma patients (as per criteria), using the Asthma control Questionnaire score (ACQ) and Exhaled nitric oxide fraction (FENO)

Age in years	Asthma patients (n=41)
Females (total and percentage)	28 (67%)
Atopy	All
Non atopy	Some
Rhinitis	None
ACQ score	2.01
FEV1 % predicted	58.5
FeNO (ppb)	30

Table 4 : Chi Square Distribution in Asthma patients

df/prob.	0.10	0.05	0.02	0.01	0.005	0.001
1	2.71	3.84	5.41	6.64	7.88	10.83
2	4.61	5.99	7.82	9.21	10.60	13.82
3	6.25	7.82	9.84	11.34	12.64	16.27
4	7.78	9.49	11.67	13.28	14.86	18.47
5	9.24	11.07	13.39	15.09	16.75	20.51

Discussion :

The significance of clinically co-relating FENO measurements with ACQ scores is that one can monitor a patient's airway inflammation by clinically predicting and diagnosing asthma control. FENO levels of patients as well as their ACQ scores are considered as benchmarks in assessing asthma control, and they both have an ability to reflect and predict the improvement or the worsening of asthma control. Asthma remains to be a national burden through patient mortality and morbidity, the rising health care costs, as well as employee absenteeism. To prescribe the correct treatment, one needs to infer the extent of airway inflammation and asthma control by assessing the FENO levels and the ACQ scores, respectively. Finding out whether FENO levels as well as ACQ scores correlate or not, can help achieve better outcomes in asthmatic patients. They can also help evaluate the outcomes of current therapeutic strategies and can help find newer emerging strategies that can help improve patients achieve asthma control.

According to the European Respiratory Journal, there has been a research on "Assessing Asthma Control: Questionnaires and Exhaled nitric oxide provide complementary information" by C. Lopes. This was the first study done to assess the contribution of FENO and Asthma Control measurement instrument for the variance of asthma

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status and to assess the contribution of FENO in the variability of asthma control using factor analysis results. A cross sectional study of 174 consecutive asthma patients was done. (82% female, 70% atopic, 76% non-smokers, and 72% using inhaled steroids). No significant co-relation was found between FENO and ACQ, while FENO and FEV1 had a weak correlation. The above data supported the hypothesis being that airway inflammation, clinical symptoms and lung function are complementary for the evaluation of asthma status in an individual. However, the cross-sectional study limited the interpretation of the results (5).

Michilis et al (6) carried out a study on "Exhaled Nitric Oxide and Asthma control: a longitudinal study in unselected patients". In this, ACQ scores and FENO values were recorded once in 341 unselected adult asthma patients. In this the whole population as well as the sub-groups were considered, both inhaled corticosteroid naïve, and low or high to medium ICS dose groups. According to the study, the exhaled nitric oxide fraction is significantly related to asthma control over time, and the overall ability of exhaled nitric oxide fraction to reflect asthma control is reduced in patients using high doses of inhaled corticosteroids.

Exhaled Nitric oxide condensate nitrates (not nitrites or FeNO) relate to Asthma Control. According to the research, exhaled nitric oxide and exhaled breath condensate NO metabolites (nitrite and nitrate) measurements are non-invasive tools to assess airway inflammation. The aim of the research was to investigate the relationship between asthma control and the mentioned bio-markers of inflammation. In the study, 39 non-smoking asthmatic patients aged 21-80 years performed FENO measurements, exhaled breath condensate nitrate (EBC nitrates), nitrites, and pH measurements. They also answered the ACQ and ACT scores. It was found that the ACT and ACQ scores had strong correlation. No relationship between ACT/ACQ score and FENO was found. EBC nitrates were found to be positively related to ACQ scores, while EBC nitrites were not found to be related to either ACT or ACQ. Therefore, EBC nitrates were found to be the only biomarker that was significantly related to asthma control, indicating a significant role of EBC nitrates in assessing asthma control (7). As already mentioned above, research has already been carried out on whether FENO measurements and ACQ values correlate or not, and it has been found that they do not tend to correlate

with each other. However, the purpose of this study was to find out whether FENO and ACQ scores correlate over a short period of time, in unselected patients of both extrinsic and intrinsic type with a large exclusion criteria of smokers, alcohol consumers, allergic rhinitis, Chronic obstructive pulmonary disease (COPD), viral infection, exercise, bronchoconstriction, etc.

Conclusion:

In conclusion, no simple linear correlation exists between FENO levels and ACQ scores in the study. Further studies with long term monitoring of management and control of atopic allergic bronchial asthma in a larger sample size correlating with adequate inhaled corticosteroids (ICS) therapy and ongoing treatment is needed to closely evaluate the link between ACQ and FENO levels. Also, only selected patients should be taken with stricter inclusion criteria of atopic-allergic bronchial asthma.

Acknowledgement :

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