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The Role of FENO in Comparison to Spirometry and ACT in Control of Children Asthma Symptoms

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ABSTRACT

Fractional exhaled nitric oxide (FeNO) is a noninvasive marker of inflammation, used for monitoring asthma. The aim of this study was to compare FeNO, asthma control test (ACT), and lung function test (spirometry) in children aged 8-15 years.

This observational, cross-sectional study was performed on76 asthmatic children (age, 8-15 years), who were referred to the Department of Immunology and Allergy, Children's Medical Center, Tehran, Iran during 2012-2013. Patients were matched for sex and age. The recruited patients were selected via consecutive sampling. FeNO was measured with a portable electrochemical analyzer and forced spirometry was performed according to the American Thoracic Society (ATS) guidelines. The ACT questionnaire was used and completed for all the patients.

The mean FeNO was 28.5±29.1 ppb, and the mean ACT score was 19.8±3.6. FeNO was significantly correlated with forced expiratory volume (FEV_1) (r, 0.232; p=0.049) or 25-75% maximum expiratory flow (MEF 25-75) (r, -0.304; p=0.009). FeNO showed no significant correlation with ACT score or FEV_1/forced vital capacity (FVC) (p>0.05). Additionally, there was no significant correlation between FeNO and changes in FEV_1 and MEF 25-75% before and after the administration of bronchodilators (p>0.05).

To improve asthma control, childhood ACT, FeNO, and spirometric tests can be used as complementary tools in clinical practice to detect children with poorly controlled asthma.

Keywords: Asthma; Child; Nitric oxide; Spirometry

INTRODUCTION

Asthma is a common chronic heterogeneous inflammatory disease of the airways, affecting 1–18% of the population in different countries.[1,2]

Nitric oxide (NO) is produced pathologically by inducible nitric oxide synthase (NOS_2) enzyme expression in eosinophil and epithelial cells of the

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airways during inhalation. It has been demonstrated that patients with asthma have high levels of NO in their exhaled breath and high levels of NOS_2 enzyme in the epithelial cells of the airways, there by suggesting the contribution of NO to the pathogenesis of asthma.[3,4]

FeNO is a biomarker of asthma, which increases along with eosinophilic airway inflammation. FeNO level is decreased dose-dependently following the use of ICS.[5,6] Serial monitoring of FeNO is useful for corticosteroid dose titration and prediction of asthma attacks.[7,8]

In addition, some studies have shown that FeNO is useful in the diagnosis of asthma.[7] Moreover, it can predict the risk of asthma attacks and act as a regulator of maintenance doses of ICS in asthma.[9,10] However, the role of FeNO in children asthma is a controversial issue among pediatricians.[11] FeNO level is variable among patients with asthma and otherwise healthy children and adults. Differences in the methodology and patient selection in different studies have been noted as the main contributing factors for these discrepancies.

Asthma monitoring tests assess disease symptoms and probable lung function.[12] Several clinical questionnaires are available to measure different levels of asthma control according to the patient's symptoms. In this regard, the asthma control test (ACT) is the most common questionnaire. The ACT is a simple and accessible tool, which can be administered quickly by patients to simplify the assessment and control of clinical asthma. The Spanish version of ACT is commonly used for adolescents, adults, and children (age, 6-11 years) in the monitoring of asthma control.[13,14]

It has been shown that the Spanish version of ACT is a reliable tool for evaluating asthma control.[15] In a previous study, a relationship was established between ACT and spirometry in Japanese children with asthma.[16] Considering the increasing prevalence of asthma, this study was performed to determine the correlation between FeNO level, PFT, and ACT in Iranian asthmatic children. We aimed to introduce an applicable and cost-effective method for better management of asthma in this age group.

MATERIALS AND METHODS

This cross-sectional, observational, descriptive study was performed on asthmatic children, aged 8-15 years, who were diagnosed based on the clinical findings and Expert Panel Report 3 (EPR3).[17] This study was approved by the Ethics Committee of Tehran University of Medical Sciences(68004). The aim of this study was explained to the parents, and written informed consents were obtained from the parents. Patients with an asthma diagnosis, who were referred to the Department of Allergy and Clinical Immunology at Children's Medical Center, Tehran, Iran (2012-2013), were included in the study. On the other hand, patients with a history of upper respiratory tract infection within3 weeks before the test, acute sinusitis, known immunodeficiency, sleep apnea, or vocal cord dysfunction were excluded. Patients were matched for sex and age variables.

All patients, who met the inclusion criteria, were enrolled via consecutive sampling until the desired sample size was achieved. In the screening visit, the patient's medical history was taken, and physical examinations were performed.

History of allergic diseases, environmental triggers, consumption of drugs or anti asthmatic medications, and body mass index (BMI) were assessed. All the patients underwent PFT via spirometry, and FeNO was also measured. At first, the ACT with 5 items, scoredon a5-point Likert scale (5 responses for each item), was completed by a physician. The total score ranged from 5 to 25 and ACT score $\geq$ 20 was considered as well-controlled asthma.

Afterward, FeNO was measured, using a NO breath FeNO device NObreath, Bedfont, UK. The FeNO level was measured based on international guidelines. The patients were asked to make a prolonged exhalation for 10 seconds at a constant flow rate after deep inhalation and to repeat this step 3 times; the average number was considered as the normal value for FeNO.[18,19] The parents were advised to avoid giving their children salbutamol (or long-acting beta-2 agonist) or carbonated beverages up to 12 hours before FeNO measurement. They were also asked to avoid any foods or liquids within2 hours before FeNO measurement. Spirometry was recommended at 30 minutes before and after receiving bronchodilators, using Zan 100 pulmonary spirometry system (nSpire, USA).[20,21]

According to the recent international guidelines, patients in the FeNO group were classified into 2 groups: <20 and ≥20 parts per billion (ppb).Then, the obtained data were recorded in the information sheets and analyzed using SPSS version 19. The mean of quantitative variables, such as age, and frequency of qualitative variables, such as sex, were also calculated.

Moreover, Chi-square test was used to compare the qualitative variables between the groups, while quantitative variables were compared using the paired *t*-test. Parametric and nonparametric tests were used to identify the relationship between FeNO and spirometric parameters.

RESULTS

Among76 patients, 49 (64.5%) were male and 27 (35.5%) were female. Comparison of demographic characteristics of patients between the FeNO groups is shown in Table 1. The mean age of the patients was 10.3±1.9 years (range, 8-15 years). The mean BMI was 19.1±3.5 kg/m^2. Based on the findings, the mean FeNO was 28.5±29.1 (range, 1-156) in asthmatic patients, and ACT score ranged from 11 to 25 (mean±SD, 19.8±3.6).

Comparison of spirometric and ACT results between the FeNO groups is shown in Table2.

Table 1. Comparison of demographic characteristics of patients with FeNO< 20 and FeNO*≥20

Variables	<20	≥20	*p*-value
Age (years)	10.05±1.8	10.7±2.10	0.165
Height (cm)	140.9±9.5	144.2±15.3	0.272
Weight (kg)	38.8±10.4	39.05±11.6	0.934
BMI (kg/m^2)	19.3±3.6	18.4±2.5	228.00.228
Sex			301.00.301
Male	59% (24)	70.6% (24)	
Female	41% (17)	29.4% (11)	
History of allergic diseases (atopic dermatitis, allergic rhinitis, and asthma)			0.003
Yes	38.5% (15)	73.5% (25)	
No	61.5%(26)	26.5% (10)	
Parental smoking			0.756
Yes	20.5% (8)	23.5% (8)	
No	7.9.5% (33)	76.5% (27)	
Inhaled steroid use			0.127
Yes	10.3% (4)	23.5% (8)	
No	89.7% (37)	76.5% (27)	
Salbutamol use			0.281
Yes	100% (41)	97.1% (35)	
No	0% (0)	2.9% (1)	

* Fractional exhaled nitric oxide (FeNO)

Table 2. Comparison of spirometric and asthma control test (ACT) data between the FeNO groups

Variables	<20	≥20	*p*-value
ACT (mean±SD)	20.7±3.3	18.8±3.8	0.022
ACT (N%) <20	(41%)16	(64.7%) 22	0.043
ACT (N%)≥20	(59%)23	(35.3%) 12	
FVC_{ex} (% predicted)	85.97±12.39	85.97±12.39	0.929
FEV_1(% predicted)	86.56±12.8	90.82±14.26	0.183
FEV_1/FVC(% predicted)	90.82±14.26	103.88±8.80	0.082
MEF 25-75(% predicted)	103.88±8.80	86.23±18.67	0.008
FVCΔ (pre/post%)	86.23±18.67	4.20±11.41	0.882
FEV_1Δ (pre/post%)	4.20±11.41	3.85±16.07	0.969
FEV_1/FVCΔ (pre/post%)	0.35±10.98	-0.20±11.92	0.834
MEF 25-75Δ (pre/post%)	6.43±21.60	8.55±27.49	0.713

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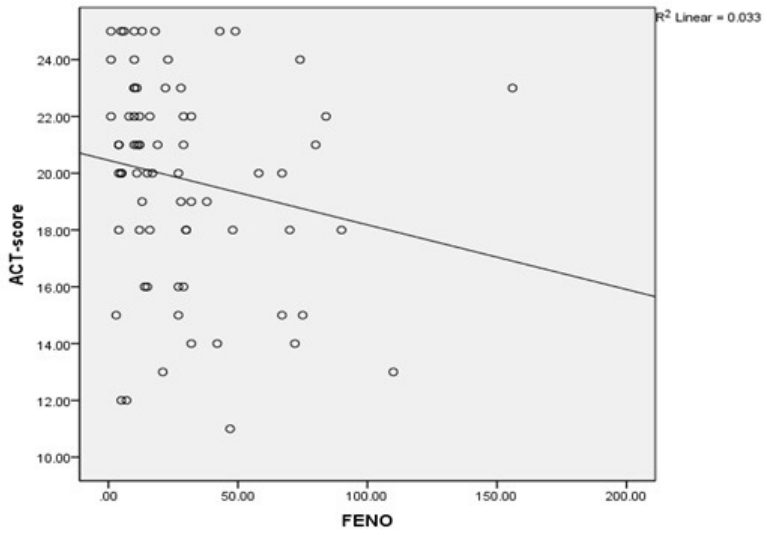

Figure 1. The correlation between fractional exhaled nitric oxide (FeNO) and asthma control test (ACT) score

In the study population, 39 (51.3%) patients had FeNO< 20 ppb and 37 (48.7%) patients had FeNO≥20 ppb. The ACT score was <20 in 40 (52.6%) patients and ≥20 in 36 (47.4%) patients. The mean FeNO was 32.05±26.9 ppb (median, 27) in patients with ACT < 20 and 24.7±31.3 ppb (median, 12) in patients with ACT≥20; however, no significant differences were observed (p=0.282).The correlation between FeNO and ACT score is shown in Figure 1 as a linear graph.

There was a significant correlation between FeNO and forced expiratory volume 1 (FEV_1) (r, 0.232; p= 0.049) (Figure2).

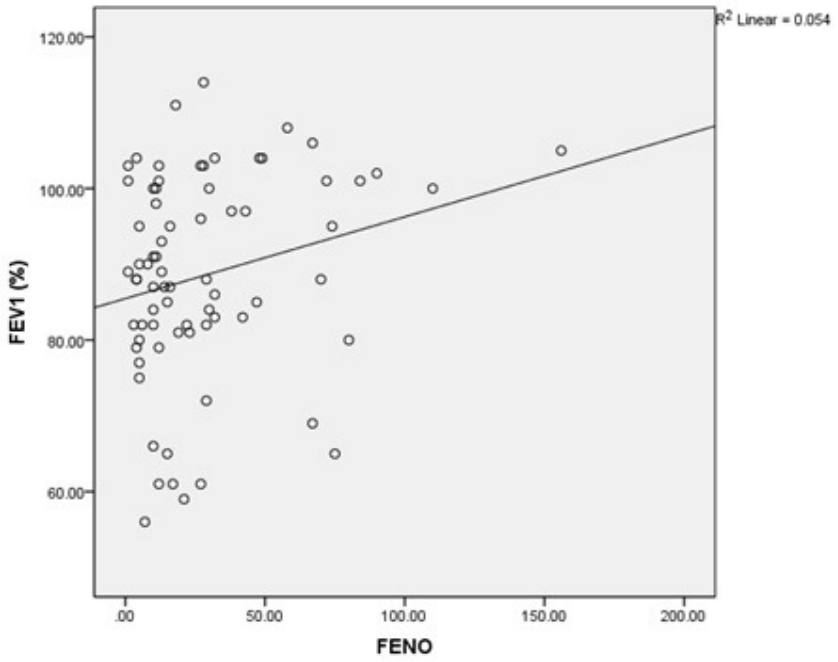

Figure 2. Correlation between fractional exhaled nitric oxide (FeNO) and forced expiratory volume 1(FEV1)

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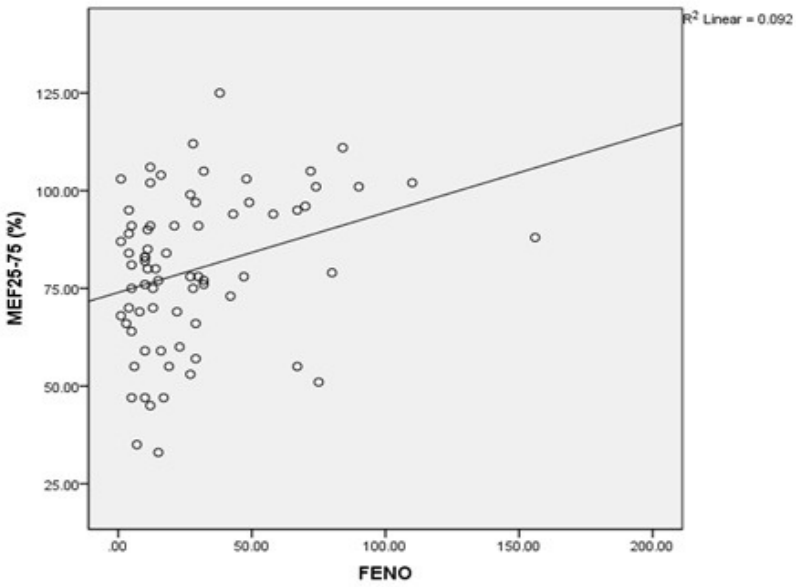

Figure 3. Fractional exhaled nitric oxide (FeNO) and maximum expiratory flow (MEF 25-75)

There was no significant correlation between FeNO and FEV_1/forced vital capacity (FVC) in the studied patients (r, 0.147; *P*=0.214); however, there was a significant relationship between FeNO and maximum expiratory flow (MEF 25-75%) (r, 0.304;*p*=0.009) (Figure 3).

The correlation between FeNO and changes in FEV_1 before and after the use of bronchodilator was not significant (r, 0.042; *p*=0.726) (Figure 4).

The correlation between FeNO and changes in MEF 25-75 before and after the use of bronchodilator was not significant (r, 0.080; *p*=0.5.3)

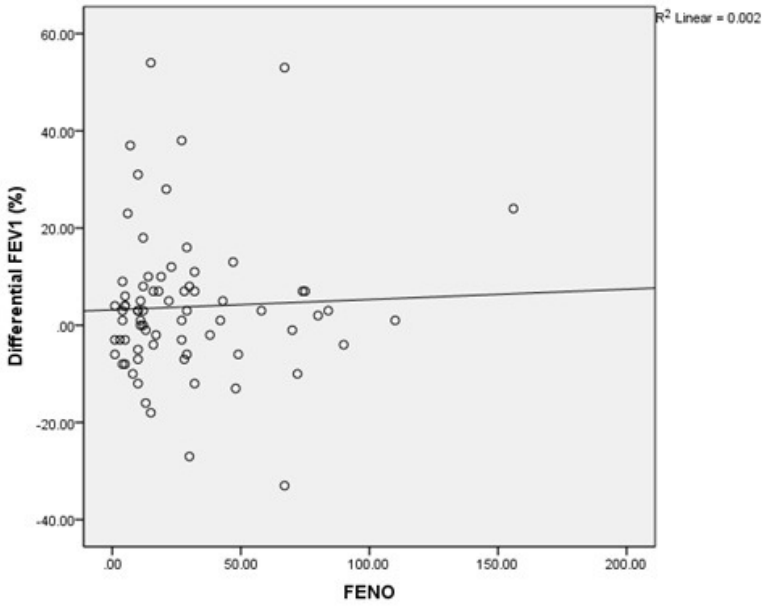

Figure 4. Fractional exhaled nitric oxide (FeNO) and changes in forced expiratory volume 1 (FEV1) before and after the use of bronchodilator

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DISCUSSION

Different international guidelines have recommended the evaluation of asthma control according to clinical symptoms and PFT results, without assessing in flammatory biomarkers.[13,14,22] In this study, the correlation between ACT, FeNO (as an eosinophilic inflammatory marker), and PFT was investigated. In this study, the ACT scores were higher in patients with FeNO<20, indicating better asthma control.

In recent clinical trials, FeNO measurement, as a complementary test, has been proposed for monitoring patients with asthma.[23] In this study, a reverse correlation was identified when comparing ACT scores with FeNO levels. In some studies, no correlation has been reported between FeNO level and asthma symptoms in the questionnaire.[9,24] whereas others have shown a correlation between ACT score and FeNO level, similar to the present study.[25,26]

In the present study, FeNO level showed a direct significant correlation with FEV_1, baseline MEF 25-75. In addition, a direct correlation was identified between FeNO level and changes in FEV_1 and MEF 25-75.In a study on 100 asthmatic patients, aged 6-86 years in the United States, no significant relationship was found between FeNO and control of asthma, which was investigated using 5different control tools such as ACT.[27]

The correlation of FeNO with ACT in asthma control has been evaluated in a few studies. In a study on 200 Italian asthmatic children, a significant relationship was found between FeNO and ACT, FEV_1, and FEV_1/FVC in patients with asthma, whereas no significant correlation was found in the follow-up.[28] The present study showed a significant direct correlation between FeNO and FEV_1, similar to some previous studies.[5,29] In contrast, some studies have not shown a significant relationship between FeNO and FEV_1.[29,30]

Moreover, no significant correlation was observed between FeNO and changes inFEV_1.In our study, the percentage of changes in pulmonary function was less than 10% at different levels of FeNO. It has been shown that FeNO cannot substitute other markers of asthma control, especially in children treated with asthma control medications.[28] In a workshop in 2012, FeNO was introduced as a complementary interventional test to assess airway diseases and asthma.[31]

For the interpretable levels of FeNO,the American Thoracic Society (ATS) guideline scan be used as a reference for interpreting FeNO in clinical settings.[32] In this study, FeNO level of 20 ppb was considered as the best predictive cut-off point, based on previous research.[27,28,32]In 35.3% of our patients with controlled asthma and ACT≥20, the FeNO level exceeded 20.It seems that even in children with mild symptoms of asthma, measurement of FeNO and other spirometric parameters is necessary. In contrast, we found that 41% of patients with uncontrolled asthma had FeNO≤20 ppb. These patients may have atopic airway inflammation, which may be related to the resistance of symptoms due to other factors, such as comorbidities, no neosinophilic asthma, or pseudo asthma.

FeNO is not a substitute measure, but a complementary tool for other airway examinations. A meta-analysis revealed that FeNO measurement is not a useful tool for identifying children with asthma in the community, as increased levels of FeNO do not discriminate patients with asthmatic and atopic symptoms. In the present study, asthma control was defined based on disease symptoms. FEV_1 independent of asthma control was in the normal range in patients with controlled or uncontrolled asthma, which is similar to previous studies.[32-34] Many asthmatic children have normal FEV_1due to the use of care facilities; this indicates that the selected cut-off point is not sufficient for the classification of asthmatic patients.[32-34]

Spirometric studies have shown that FEV_1 has no significant correlation with the symptoms or severity of clinical disease in children, and only FEV_1/FVC showed a poor relationship with the symptoms. Therefore, it seems that recent guidelines can only lead to suboptimal asthma control.[35] These findings are similar to the results of our study, indicating that disease symptoms, spirometry, and FeNO should be considered in asthma control.

In line with some previous research, the current study showed that FeNO is a noninvasive marker of airway inflammation, and its measurement can be helpful in the diagnosis of allergic asthma.[36,37] In addition, FeNO is useful in predicting the clinical outcomes in terms of response to steroid therapy and asthma attacks. Some studies have shown that FeNO is used as a sensitive inflammatory marker to evaluate responses to anti-inflammatory therapy.[38,39]

Finally, we acknowledge that this study has some limitations. For example, we did not record of comorbidities in our patients, such as gastroesophageal reflux disease, and some confounding variable such as air pollution in our patients.

According to the results of the present study, FeNO measurement is useful for monitoring and management of asthma symptoms in children, similar to PFT and ACT. We suggest future studies with larger sample size and a higher FeNO cut-off point as the reference value. In addition, further studies are recommended on patients with asthma, and follow-up is suggested for a specific period.

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