# The relationship between the fraction of exhaled nitric oxide and the level of asthma control

## La relation entre la fraction exhalée du monoxyde d'azote et le niveau de contrôle de l'asthme

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**RÉSUMÉ**

**Introduction:** L'évaluation du contrôle de l'asthme, basée sur les symptômes et les facteurs de risque d'exacerbation, ne fournit aucune information sur l'inflammation des voies respiratoires, reflétée par la fraction exhalée du monoxyde d'azote (FeNO). L'impact du FeNO dans l'évaluation de la maîtrise de l'asthme n'a pas été bien évalué. L'objectif de cette étude était d'évaluer la contribution de la mesure de FeNO dans l'évaluation du contrôle de l'asthme.

**Méthodes:** Une étude transversale prospective a été réalisée pendant quatre mois et portait sur 148 asthmatiques adultes. Pour chaque patient, les données démographiques, le score de l'Asthma Control Test (ACT), l'adhérence au traitement, la positivité des tests cutanés, le niveau de la FeNO et les résultats de spirométrie ont été relevés. La corrélation entre le score de l'ACT et la valeur de la FeNO a été analysée.

**Résultats:** Le score moyen de l'ACT était de 20,9±3,7 et la valeur moyenne de la FeNO exhalé était de 30,4±25,8 ppb. L'asthme était contrôlé chez 71,6% des patients. Les valeurs moyennes de la FeNO étaient significativement plus élevées chez les patients asthmatiques non contrôlés (42,1±30,8 vs 27±19 ppb, p=0,01). Une corrélation négative significative a été observée entre la valeur de la FeNO et le score de l'ACT (r=-0,33, intervalle de confiance à 95% [IC], -0,51-0,10; p=0,001). La FeNO avait une valeur prédictive négative (79,9%) et une spécificité (63,2%) élevées, mais une sensibilité (59,5%) et une valeur prédictive positive (39%) faibles. L'air sous la courbe ROC était de 0,7 (intervalle de confiance à 95% [IC], 0,53-0,74; p = 0,01).

**Conclusions**: L'utilisation de la FeNO uniquement pour évaluer le contrôle de l'asthme représente une approche limitée en raison de la faible valeur prédictive positive pour le diagnostic de l'asthme non contrôlé.

**Mots-clés**

Asthme, Asthma Control Test, monoxyde d'azote exhalé, inflammation des voies aériennes.

**SUMMARY**

**Background:** The evaluation of asthma control, based on symptoms and risk factors for exacerbation does not provide information about airway inflammation, reflected by fractional exhaled nitric oxide (FeNO). The impact of FeNO in the evaluation of asthma control has not been well recognized. The purpose of this study was to evaluate the contribution of FeNO measurement in the assessment of asthma control.

**Methods:** A prospective cross-sectional study was carried out for four months and included 148 adult asthmatics. For each patient, the demographic data, asthma control test (ACT) score, medication adherence, skin prick test positivity, FeNO level, and spirometry results were recorded independently. The correlation between ACT score and FeNO level was analyzed.

**Results:** The mean ACT score was 20.9±3.7 and the mean exhaled FeNO level was 30.4±25.8 ppb. Asthma was controlled in 71.6% of patients. Mean FeNO values were significantly higher in patients with uncontrolled asthma (42.1±30.8 versus 27±19 ppb, p=0.01). A significant negative correlation was observed between FeNO level and ACT score (r=-0.33, 95% confidence interval [CI], -0.51-0.10; p=0.001). FeNO had a high negative predictive value (79.9%) and specificity (63.2%), but a low sensitivity (59.5%) and positive predictive value (39%). The area under the receiver operating characteristic (ROC) curve was of 0.7 (95% confidence interval [CI], 0.53-0.74; p=0.01).

**Conclusions:** Using just FeNO to evaluate asthma control represents a limited approach because of the low predictive accuracy of FeNO for diagnosing uncontrolled asthma.

**Key-words**

Asthma, Asthma control test, exhaled nitric oxide, airway inflammation.

## INTRODUCTION

Asthma is characterized by different clinical features and numerous phenotypes expression. Each phenotype expression can have a specific combination of control parameters. Since airway inflammation is the key to the physiopathological process in asthma, asthma control cannot be assessed only by clinical parameters based on subjective symptoms. It would be practical to incorporate the measure of airway inflammation. In the clinical practice, the level of airway inflammation is reflected by fractional exhaled nitric oxide (FeNO) level. FeNO is a noninvasive biomarker of airway inflammation which is increased in steroid-naive asthma (1). High FeNO is interrelated with the degree of bronchial hyperresponsiveness and eosinophilic airway inflammation and is decreased with inhaled corticosteroids (2). It is validated by the American Thoracic Society guidelines for the diagnosis of eosinophilic asthma (3). However, the optimization of asthma treatment by FeNO monitoring has not been well recognized. According to GINA guidelines, evaluation of asthma control did not include FeNO level (4). The contribution of FeNO monitoring in asthma management was suggested by some studies. However, none were statistically convincing due to different methodology and study populations heterogeneity (5,6). Nevertheless, several self-administered surveys were developed to evaluate asthma control in clinical practice. One of the two most common questionnaires used to evaluate asthma control is the Asthma Control Test (ACT), developed by Nathan (7) in 2004 and recently was translated into Arabic (8).

The objective of this study is to assess the contribution of FeNO measurement in the evaluation of asthma control by analyzing the correlation between Asthma Control Test (ACT) and FeNO in adult asthmatics.

## METHODS

### - Study design

A prospective cross-sectional study was carried out from May to August 2017 in the external consultations of pulmonology and allergology department of The Tunisian Ministry of Interior hospital in Tunis. Data were collected during regular medical procedures. The ethics of the hospital's committee were respected as well as the patients' verbal consent.

The results were recorded independently for each patient as well as the demographic data, ACT score, medication adherence, skin prick test positivity, FeNO level, and spirometry.

### Study population and procedures

Inclusion criteria included female and male subjects, older than 15 years, taking anti-asthma treatment, either using or not using inhaled corticosteroid therapy with other asthma's medications, for at least three months before the study. Asthma was diagnosed according to GINA guidelines (4).

The non-inclusion criteria involved upper or lower respiratory infection three weeks before the visit, current or past smokers with accumulated consumption more than 5 pack year, poor medication adherence and other chronic respiratory diseases.

Patients with poor compliance with FeNO measurements or spirometry techniques were excluded from the study.

### Study Procedures

**-** Asthma Control test

The ACT-Arabic version was used to evaluate asthma control (8). Well-controlled asthma is defined by an ACT score above 19.

- Exhaled nitric oxide fraction

FeNO measurement was performed at a flow rate of 50 ml/s using HYPER FeNO® chemoluminescence nitric oxide analyzer (Medisoft). The maneuver consists of a single measurement during the exhalation from the total lung capacity. This procedure was performed and interpreted according to the American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations (3). The maneuver was repeated three times. The reproducible value with a difference of less than 5% of the previous one was used for analysis. Absolute FeNO values are expressed in parts per billion (ppb). The absence of airway inflammation is defined by a FeNO value below 25 ppb. FeNO was measured before spirometry.

- Pulmonary function test

Patients performed spirometry using a VMAX spirometer (Sensormedics). Spirometry was carried out and interpreted according to the ATS/ERS guidelines (9). The best of the three results was used, as determined by the highest forced expiratory volume in 1 second (FEV1). The baseline and post-bronchodilator forced vital capacity (FVC) and FEV1 were expressed as absolute values and percentage of predicted values. FEV1/FVC was calculated for each patient. Changes in FEV1 and FVC

after reversibility test with bronchodilator are expressed as a percentage of the initial value.

- Allergic sensitization test

The allergic sensitization test was done using a skin prick test for common aeroallergens.

**- Study endpoints**

The primary endpoint was the comparison between mean FeNO in controlled and uncontrolled asthmatics and the evaluation of correlation degree between ACT and FeNO. The secondary endpoint was checking the ability of high FeNO to predict uncontrolled asthma. To achieve this endpoint, sensitivity, specificity, positive and negative predictive values of FeNO and area under the receiver operating characteristic (ROC) curve were calculated.

**- Statistical methods**

Qualitative variables data were expressed as percentages. Quantitative variables were expressed as means and standard deviations (SD). The Pearson coefficient was used to assess the linear correlation between ACT scores and levels of FeNO. Student's t-test and Chi-square test were used respectively to compare means and percentages. P values less than 0.05 were considered statistically significant. The ROC data were used to estimate the area under the curve (AUC). This cut-off value was used to obtain sensitivity, specificity, positive predictive values and negative predictive values to the whole population. Statistical Package for Social Science (SPSS version 20.00) was used to analyze the quantitative and the qualitative data obtained.

## RESULTS

We included 148 patients with complete data in the study. The mean age was 44.2±14.7 years and 55.4% of subjects were female. The average asthma follow-up period was 115 months. Table1 shows that the majority of the patients had a history of allergic rhinitis (77%). The mean FEV1 was 86% of predicted value with values above 80% in 70.9% of included patients. Airflow obstruction was observed in 37.1% of patients. The mean ACT score was 20.9±3.7 and the mean exhaled FeNO level was 30.4±25.8 ppb.

Medium dose inhaled corticoids was prescribed in 87% of patients and high dose in 13% of them.

According to the ACT score, 71.6% of patients had controlled asthma. Mean FeNO values were higher in patients with an ACT score <20 (42.1±30.8 ppb) in comparison to those with an ACT score ≥20 (27±19 ppb, p=0.01).

**Table 1:** General characteristics of asthma patients

| General characteristics | |
|---|---|
| Number | 148 |
| Age (years) | 44.2 ± 14.8 |
| BMI (kg/m$^2$) | 26.8 |
| Women, n (%) | 82 (55.4) |
| Smoking status, n (%) | |
| - Never smoked | 110 (74.3) |
| - Current smoker | 8 (5.4) |
| - Past smoker | 30 (20.2) |
| Asthma follow-up (years) | 9.5 |
| Allergic history, n (%) | |
| - Allergic rhinitis | 115 (77) |
| - Allergic conjunctivitis | 71 (48) |
| - Atopic dermatitis | 14 (10) |
| Positive skin test, n (%) | 101 (68.2) |
| Spirometry | |
| - FEV1, % of predicted | 86 |
| - FEV1≥80%, n (%) | 105 (70.9) |
| - Normal, n (%) | 55 (37.1) |
| - Airflow obstruction | 47 (31.7) |
| - Small airways obstruction | 46 (31) |
| ACT score, | 20.9 ± 3.7 |
| FeNO (ppb) | 30.4±25.8 |

Abbreviations: BMI: body mass index, FEV1: forced expiratory volume in one second, ACT: asthma control test, FeNO: fractional exhaled nitric oxide

High FeNO level was observed in 37% of patients with controlled asthma and normal FeNO level was found in 40.5% of uncontrolled asthmatics (Table 2). Linear regression analysis showed a negative correlation of FeNO with ACT score (r=-0.33, 95% confidence interval [CI], -0.51-0.10; p=0.001) (Figure 1).

The distribution of FeNO levels referred to asthma control status showed that FeNO higher than 25 ppb had 59.5% sensitivity and 39% positive predictive value to identify patients with uncontrolled asthma. The specificity was 63.2% and the negative predictive value was 79.7%.

The evaluation of the ability of FeNO to diagnose uncontrolled asthma as determined by ACT score revealed an area under the ROC curve of 0.7 (95% confidence interval [CI], 0.53–0.74; p=0.01) (Figure 2).

**Table 2:** Characteristics for controlled and uncontrolled asthma patients according to the ACT score

| | Controlled asthma (ACT score <20) | Uncontrolled asthma (ACT score ≥20) | p |
|---|---|---|---|
| Number, n (%) | 106 (71.6) | 42 (28.3) | |
| Age, years | 44.7±14 | 42.8±15 | 0.4 |
| Gender ratio | 0.8 | 0.75 | 0.3 |
| BMI (kg/m2) | 26.7 | 26.9 | 0.1 |
| Smoking status, n (%) | | | |
| - Never smoked | 77 (72.6) | 33 (78.5) | 0.45 |
| - Current smoker | 5 (4.7) | 3 (7.1) | 0.55 |
| - Past smoker | 24 (22.6) | 6 (14.2) | 0.25 |
| Allergic history, n (%) | | | |
| - Allergic rhinitis | 85 (80) | 30 (71.4) | 0.24 |
| - Allergic conjunctivitis | 52 (49) | 19 (45.2) | 0.67 |
| - Atopic dermatitis | 8 (8) | 6 (14.2) | 0.2 |
| Positive skin test, n (%) | 71 (67) | 30 (71.4) | 0.6 |
| Spirometry | | | |
| - FEV1, % of predicted | 88 | 80 | 0.005 |
| - FEV1≥80%, n (%) | 78 (73.5) | 27 (64.2) | 0.26 |
| - Normal, n (%) | 46 (43.3) | 9 (21.4) | 0.01 |
| - Airflow obstruction | 24 (22.6) | 23 (54.7) | $<10^{-3}$ |
| - Small airways obstruction | 36 (33.9) | 10 (23.8) | 0.22 |
| Mean FeNO (ppb) | 27±19 | 42,1±30,8 | 0.01 |
| FeNO<25 (ppb), n (%) | 67 (63) | 17 (40.5) | 0.01 |
| FeNO [25-50] (ppb), n (%) | 29 (27.3) | 16 (38) | 0.2 |
| FeNO >50 (ppb), n (%) | 10 (9.4) | 9 (21.5) | 0.04 |

Abbreviations: BMI: body mass index, FEV1: forced expiratory volume in one second, ACT: asthma control test, FeNO: fractional exhaled nitric oxide.

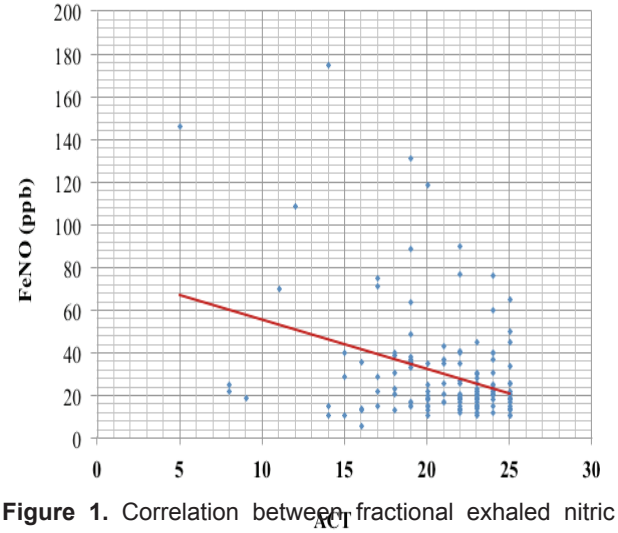


**Figure 1.** Correlation between fractional exhaled nitric oxide (FeNO) levels and asthma control test (ACT) scores: r=-0.33, 95% confidence interval [CI], -0.10,-0.51; p=0.001.

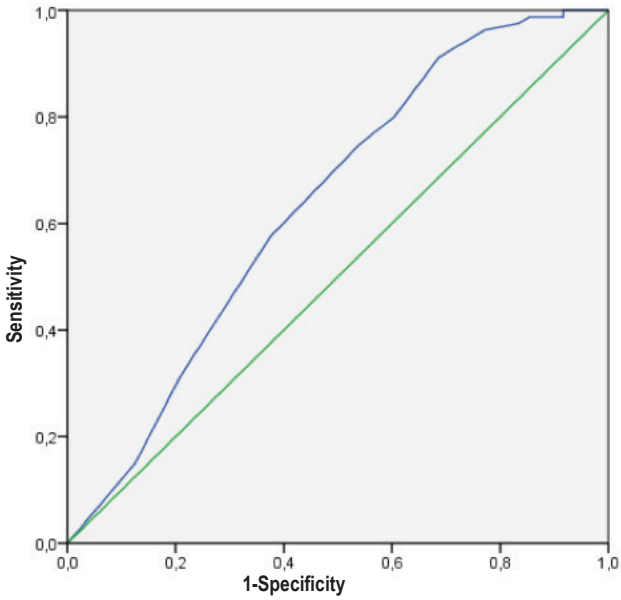


**Figure 2.** Receiver operating curves (ROC) characterizing the ability of fractional exhaled nitric oxide to assess asthma control; area under the ROC curve of 0.7 (95% confidence interval [CI], 0.53–0.74; p=0.01).

## DISCUSSION

Our study revealed the poor concordance between self-assessment of asthma control by the ACT and FeNO. We found a weak negative linear relationship between FeNO and ACT despite that FeNO was significantly higher in patients with uncontrolled asthma. Elevated exhaled nitric oxide has a high negative predictive value to predict the good level of asthma control. The evaluation of data by ROC analysis confirmed that FeNO level has a moderate reliability to diagnose uncontrolled asthma as determined by the ACT.

It was demonstrated that ACT of ≤19 had a sensitivity ranging between 69 and 93.9% to predict uncontrolled asthma (7,10) and an ACT score ≥20 predicted controlled asthma in 51.3% of cases (10).

According to these studies, ACT is a useful tool for evaluating asthma control in comparison to GINA guidelines. It is a simple way to detect uncontrolled asthma in routine clinical practice. However, for patients with an ACT ≥20, this test remains incomplete because it overestimates the control of asthma in one out of two patients.

In addition, characteristics defining asthma control are subjective and rely on patient's descriptions. It would be helpful for clinicians to have objective means of asthma control assessment other than the ACT which allows for better detection of controlled asthma.

FeNO is a noninvasive biomarker for the evaluation of airway inflammation. FeNO can be used to predict asthma exacerbations (11), to reduce inhaled corticosteroids without altering asthma control (12) and to lower the cost of asthma management with more effective treatment decisions by identifying among uncontrolled asthmatics those who not require an increase in inhaled corticosteroids (13).

It was demonstrated that FeNO is significantly higher in patients with uncontrolled asthma (14–16). This result is in accordance with the result of the present study. Thus, finding high FeNO levels in treated asthmatics may reflect a lack of asthma control. Nevertheless, we found that 37% of patients with well-controlled asthma had high FeNO and 40.5% of patients with uncontrolled asthma had normal FeNO. LaForce and coll (13) showed that 42.9% of patients with well-controlled asthma had high FeNO and 58.6% of patients with uncontrolled asthma had normal FeNO. This discrepancy was explained by several factors that may interact with FeNO level in asthmatics. Some of these factors are associated with asthma characteristics and others are more general.

The presence of normal FeNO in uncontrolled asthmatics can be explained by the role of non-inflammatory asthma triggers, such as cold air and exercise, that do not lead to an increase in FeNO (17). Furthermore, the neutrophilic airway inflammation asthma phenotype prohibits the increase of FeNO in uncontrolled asthmatics. It was demonstrated that FeNO was higher in asthmatics with eosinophilic and mixed phenotype than those with neutrophilic and low inflammation phenotype (18).

Further factors were responsible for FeNO decreases such as inhaled corticosteroids (19,20), nitrate-rich meal (21) and active smoking (2). In this study, 87% of patients are tacking medium dose inhaled corticoids which can explain the normal value of FeNO in 40.5% of patients with uncontrolled asthma.

Nevertheless, other factors are responsible for an increase of FeNO level in controlled asthmatics, such as atopy (22–24) and age and height especially in children (25,26).

Thus, using just FeNO to evaluate asthma control represents a limited approach, since several factors may vary FeNO level. For this reason, it is suitable to associate FeNO with other means for asthma control assessment.

As it has been shown, ACT overestimates the control of asthma in one out of two patients for patients with an ACT score ≥20. Therefore, the addition of ACT to FeNO may be a good approach to assess asthma control.

As found in the present study, many other works showed a weak correlation between FeNO and clinical parameters (14,27–30) and low predictive accuracy of FeNO for diagnosing uncontrolled asthma (17). The weak correlation between FeNO and ACT could be explained by inhaled corticosteroids.

However, a significant correlation has been found in other studies such as Senna and coll (31) which evaluated the correlation of FeNO with FEV1 and ACT score in 27 patients recently diagnosed with asthma and found a significant relationship between FeNO and ACT ($r=0.69$, $p=0.001$). Nevertheless, the small number of subjects included and the asthma control assessment in newly diagnosed and not treated asthmatics were the principal limitations of this study. A high link between ACT scores and FeNO was also found by Habib and coll (15). Nonetheless, the small size of the sample, the exclusion of patients with allergic rhinitis and the use of FeNO cut-off point of 47 ppb biased the results.

According to these studies, it is difficult to conclude on the relationship between FeNO and asthma control due to contradictory results. Published studies have several limitations that do not allow the generalization of these results. The principal limitation of FeNO studies is age heterogeneity of study population including both children and adults. The evaluation of asthma control is particularly difficult for children requiring the use of an adapted ACT (32), and reference values of FeNO are different from an adult with a fixed cut-off point at 20 ppb for children under 12 (3).

Several other biases limit the validity and relevance of these works, such as small sample size, the variability of asthma follow-up period, inadequate statistical analyses (unspecified confidence intervals) and the lack of standard reference values for FeNO measurements.

The limitations of our study are its cross-sectional design, the small sample size, the extended follow-up period of asthma patients and the high percentage of patients with well-controlled asthma. Moreover, FeNO norms in healthy Tunisian adults are different from reference values used in this work, with a fixed cut-off point at 34 ppb (33).

Further longitudinal prospective studies with a larger sample size are needed and may provide much more valuable information than single measurement in the assessment of asthma control. Therefore, changes in FeNO levels were more useful than single cut-off points in predicting and diagnosing loss of asthma control (20,34).

## CONCLUSIONS

The results of this study showed that FeNO has a discriminative capacity between controlled and uncontrolled asthmatics. Exhaled nitric oxide has a good negative predictive value reflecting a good ability to predict well-controlled asthma. However, using FeNO as a single mean for asthma control assessment may have limitations. For this reason, Global Initiative for Asthma (GINA) has not recommended the FENO-guided therapy for the “general” asthma population. Thus it is widely considered to identify subsets of asthma patients that would receive benefits from the FENO-guided therapy.

## REFERENCES


1. Alving K, Weitzberg E, Lundberg JM. Increased amount of nitric oxide in exhaled air of asthmatics. Eur Respir J. 1993 Oct;6(9):1368–70.
2. Kharitonov SA, Robbins RA, Yates D, Keatings V, Barnes PJ. Acute and chronic effects of cigarette smoking on exhaled nitric oxide. Am J Respir Crit Care Med. 1995 Aug;152(2):609–12.
3. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med. 2011 Sep 1;184(5):602–15.
4. (*NEW) 2017 GINA Report: Global Strategy for Asthma Management and Prevention [Internet]. Global Initiative for Asthma - GINA. [cited 2017 Apr 27]. Available from: http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/
5. Petsky HL, Cates CJ, Lasserson TJ, Li AM, Turner C, Kynaston JA, et al. A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils). Thorax. 2012 Mar;67(3):199–208.
6. Petsky HL, Cates CJ, Li A, Kynaston JA, Turner C, Chang AB. Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006340.
7. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004 Jan;113(1):59–65.
8. Lababidi H, Hijaoui A, Zarzour M. Validation of the Arabic version of the asthma control test. Ann Thorac Med. 2008 Apr;3(2):44–7.
9. Laszlo G. Standardisation of lung function testing: helpful guidance from the ATS/ERS Task Force. Thorax. 2006 Sep;61(9):744–6.
10. Thomas M, Kay S, Pike J, Williams A, Rosenzweig JRC, Hillyer EV, et al. The Asthma Control Test (ACT) as a predictor of GINA guideline-defined asthma control: analysis of a multinational cross-sectional survey. Prim Care Respir J J Gen Pract Airw Group. 2009 Mar;18(1):41–9.
11. Harkins MS, Fiato K-L, Iwamoto GK. Exhaled nitric oxide predicts asthma exacerbation. J Asthma Off J Assoc Care Asthma. 2004 Jun;41(4):471–6.
12. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med. 2005 May 26;352(21):2163–73.
13. LaForce C, Brooks E, Herje N, Dorinsky P, Rickard K. Impact of exhaled nitric oxide measurements on treatment decisions in an asthma specialty clinic. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. 2014 Dec;113(6):619–23.
14. Shirai T, Furuhashi K, Suda T, Chida K. Relationship of the asthma control test with pulmonary function and exhaled nitric oxide. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. 2008 Dec;101(6):608–13.
15. Habib SS, Alzoghaibi MA, Abba AA, Hasan M. Relationship of the Arabic version of the asthma control test with ventilatory function tests and levels of exhaled nitric oxide in

adult asthmatics. Saudi Med J. 2014 Apr;35(4):397–402.
16. Delgado-Corcoran C, Kissoon N, Murphy SP, Duckworth LJ. Exhaled nitric oxide reflects asthma severity and asthma control. Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc. 2004 Jan;5(1):48–52.
17. Khalili B, Boggs PB, Shi R, Bahna SL. Discrepancy between clinical asthma control assessment tools and fractional exhaled nitric oxide. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. 2008 Aug;101(2):124–9.
18. Shimoda T, Obase Y, Nagasaka Y, Nakano H, Kishikawa R, Iwanaga T. Airway inflammation phenotype prediction in asthma patients using lung sound analysis with fractional exhaled nitric oxide. Allergol Int [Internet]. 2017 Mar [cited 2017 Jul 15]; Available from: http://linkinghub.elsevier.com/retrieve/pii/S1323893017300205
19. Anderson WJ, Short PM, Williamson PA, Lipworth BJ. Inhaled corticosteroid dose response using domiciliary exhaled nitric oxide in persistent asthma: the FENOtype trial. Chest. 2012 Dec;142(6):1553–61.
20. Michils A, Baldassarre S, Van Muylem A. Exhaled nitric oxide and asthma control: a longitudinal study in unselected patients. Eur Respir J. 2008 Mar;31(3):539–46.
21. Olin AC, Aldenbratt A, Ekman A, Ljungkvist G, Jungersten L, Alving K, et al. Increased nitric oxide in exhaled air after intake of a nitrate-rich meal. Respir Med. 2001 Feb;95(2):153–8.
22. Lúdvíksdóttir D, Janson C, Högman M, Hedenström H, Björnsson E, Boman G. Exhaled nitric oxide and its relationship to airway responsiveness and atopy in asthma. BHR-Study Group. Respir Med. 1999 Aug;93(8):552–6.
23. Franklin PJ, Turner SW, Le Souëf PN, Stick SM. Exhaled nitric oxide and asthma: complex interactions between atopy, airway responsiveness, and symptoms in a community population of children. Thorax. 2003 Dec;58(12):1048–52.
24. Ho LP, Wood FT, Robson A, Innes JA, Greening AP. Atopy influences exhaled nitric oxide levels in adult asthmatics. Chest. 2000 Nov;118(5):1327–31.
25. Malmberg LP, Petäys T, Haahtela T, Laatikainen T, Jousilahti P, Vartiainen E, et al. Exhaled nitric oxide in healthy nonatopic school-age children: determinants and height-adjusted reference values. Pediatr Pulmonol. 2006 Jul;41(7):635–42.
26. Buchvald F, Baraldi E, Carraro S, Gaston B, De Jongste J, Pijnenburg MWH, et al. Measurements of exhaled nitric oxide in healthy subjects age 4 to 17 years. J Allergy Clin Immunol. 2005 Jun;115(6):1130–6.
27. Álvarez-Gutiérrez FJ, Medina-Gallardo JF, Pérez-Navarro P, Martín-Villasclaras JJ, Etchegoren BM, Romero-Romero B, et al. Relationship of the Asthma Control Test (ACT) with Lung Function, Levels of Exhaled Nitric Oxide and Control According to the Global Initiative for Asthma (GINA). Arch Bronconeumol Engl Ed. 2010 Jul;46(7):370–7.
28. Han C-H, Park Y-I, Kwak HJ, Kim SI, Kim TH, Sohn JW, et al. Relationship between Exhaled Nitric Oxide and Levels of Asthma Control in Asthma Patients Treated with Inhaled Corticosteroid. Tuberc Respir Dis. 2011;71(2):106.
29. Bora M, Alpaydin AO, Yorgancioglu A, Akkas G, Isisag A, Coskun AS, et al. Does asthma control as assessed by the asthma control test reflect airway inflammation? Multidiscip Respir Med. 2011 Oct 31;6(5):291–8.
30. Sato S, Saito J, Fukuhara A, Uematsu M, Suzuki Y, Togawa R, et al. The clinical role of fractional exhaled nitric oxide in asthma control. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. 2017 Dec;119(6):541–7.
31. Senna G, Passalacqua G, Schiappoli M, Lombardi C, Wilcock L. Correlation among FEV, nitric oxide and asthma control test in newly diagnosed asthma. Allergy. 2007 Feb;62(2):207–8.
32. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol. 2007 Apr;119(4):817–25.
33. Sfaxi I, Ben Saad H, Rouatbi S. Fraction of exhaled nitric oxide in healthy elderly Tunisian subjects. Nitric Oxide. 2015 Nov 15;50:88–97.
34. Jones SL, Kittelson J, Cowan JO, Flannery EM, Hancox RJ, McLachlan CR, et al. The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. Am J Respir Crit Care Med. 2001 Sep 1;164(5):738–43.