The Role of Serum IL-1β in Combination with Fractional Exhaled Nitric Oxide in the Diagnosis of Adult Bronchial Asthma

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Abstract

Background: Asthma is a chronic airway disorder, in which cytokines are probably contributing in the inflammation and in the pathophysiology of the disease. This study aimed to determine the benefit of measurement of FENO and IL-1β in the diagnosis of asthma.

Method: The study was conducted in Merjan Medical City and Spiro private clinic in Babylon province in the period from March to June 2019, 127 asthmatic patients were compared with 60 healthy subjects as control group. The age ranged from 10 to 60 years old, fractional exhaled nitric oxide (FENO) test was performed to assess asthma by using (Medisoft® company, Belgium). Body mass index (BMI) was subtracted as weight (kg)/height (m^2). Waist circumference/cm (WC) was calculated between the inferior margin of thoracic ribs and midline of the iliac-crest. Hip circumference/cm (HC) was calculated from the broadest hip eminent before the waist/hip ratio (W/H) computed. The FENO measures had classified into low (<25 ppb) or intermediate-high (⩾25 ppb) according to the ''American Thoracic Society recommendations''. Iterleukine-1 beta (IL-1β) was measured in the sera by ELISA technique using Human IL-1β (Interleukin 1-Beta) ELISA Kit from Elabscience®.

Results: there was no significant correlation between the levels of FENO and IL-1β with body weight as measured by the way of BMI and waist/hip ratio. There was no correlation between duration of asthma with the levels of FENO and IL-1β. ROC curve analysis of FENO test in BA patients showed significant (p-0.001) high sensitivity (92%) and specificity (90%). However, ROC curve analysis of IL-1β in BA patients revealed non-significant (p-0.53), lower accuracy (56.4%), sensitivity 962%) and specificity (57%) to distinguish BA patients).

Conclusion: No relation between obesity and eosinophilic airways inflammation. The measurement of FENO level is more important in assessment of asthma inflammation than IL-1β.

Key Words: Asthma, FENO, IL-1β, Interleukin, Fractional Exhaled Nitrous Oxide.

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Introduction

Currently the fractionated exhaled nitric oxide (FENO) test has been anticipated as a noninvasive procedure for valuation of asthmatic bronchial-inflammatory response (Qasim J., 2020). The incidence of asthma as a communal, long-lasting illness may reach 5% in industrial states. Asthma categorized as a continuing inflammatory, hyper-responsive and generally reversible bronchial obstruction (Amjed H., 2021, Qasim J., 2020). Clinically, pulmonary-spirometer can considered as a classical test for diagnosing obstructed airways and its accurate measure to assess asthma severity (Fitzpatrick, 2015).

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Above all, the obstruction of respiratory airways is frequently not insistent in the mild form of asthma that results to diagnostic ambiguity (Kim et al., 2015). As a chronic inflammatory pathology, the precise role of cytokine in the pathogenesis of bronchial asthma is still indefinite (Hoffman and Wanderer, 2010). Even though cytokines are at the fundamental of newly develop asthma medications, little is identified regarding the link of circulating cytokine concentrations with asthma outcomes (Bai et al., 2019).

Increased FENO results has been reliably verified in asthma even in mild phenotypes (de Abreu et al., 2019). Consequently, FENO measures could confirm asthma diagnosis. FENO can establish rapid and careful asthma-diagnosis in general and private practice without carrying out provocative bronchial tests (de Abreu et al., 2019, Franklin and Stick, 2008). The analytic exactness of FENO in asthma has been inspected in several revisions. The outcomes were mostly promising, in spite of quite dissimilar cutoff points of asthma precision have been described (Dweik et al., 2011).

Interleukin (IL)-1β is a leukocyte endogenous cytokine has pro- and anti-inflammation effect, that highly considered in modulating the inflammation and ensuing pathological changes in response of ''airway smooth muscle (ASM)'' of asthma (Scott et al., 2010). Bronchial inflammation, higher agonist-mediated bronchospasm and weakened sympathetic-mediated airway relaxation are distinguishing findings in asthma (Hilvering and Pavord, 2015).

IL-1β is a crucial cytokine primarily intricate in local and systemic inflammatory reactions (Liang et al., 2016). The available evidences revealed that dysregulated IL-1β productions and extended release in chronic inflammatory illnesses, including inflammatory bowel syndrome, psoriasis and rheumatoid arthritis, may subsidize to their pathogenesis (Arend and Guthridge, 2000). Additionally, IL-1β is responsible for the initial phases of the inflammation and hyperresponsiveness of asthmatic airways. Raised concentrations of IL-1β cytokine have been exposed in the airways of asthma individuals (Gao et al., 2015). Moreover, there is an increasing evidence displaying that IL-1β modifies airway constriction and dilatation via direct effect on the bronchial muscles (Clerisme-Beaty et al., 2009). These evidences highpoints the significant contribution of IL-1β in the asthma pathogenesis (Novosad et al., 2013). This study aimed to determine the benefit of measurement of FENO and IL-1β in the diagnosis of asthma.

Patients and Method

The study was performed in Merjan Medical City and Spiro private clinic in Babylon province in the period from March to June 2019. It had included 127 asthmatic patients with 60 healthy subjects as control group. The age of the participants ranged from 10 to 60 years old, and the males were dominant in this study. The asthma had assessed using FENO test using (Medisoft® company, Belgium). FENO concentrations had assessed in accordance to the guidelines of the American Thoracic Society (ATS) using the single breath technique, repetitive expirations were completed to achieve triple NO measures that approved at the 5% concentration. NO levels verified as the average of the triple measures. Body mass index (BMI) was subtracted as weight (kg)/height (m2). Waist circumference/cm (WC) had calculated between the inferior margin of thoracic ribs and midline of the iliac-crest. Hip circumference/cm (HC) had calculated from the broadest hip eminent before the waist/hip ratio (W/H) being computed. The results of FENO rests had grouped to low and intermediate/high (<25ppb and⩾25ppb), respectively according to the ATS references. Measurement of IL-1β in the sera had performed by ELISA technique using Human IL-1β (Interleukin 1-Beta) ELISA Kit from Elabscience® with a detection Range: 7.81~500 pg/mL and a sensitivity of: 4.69 pg/ml.

Ethical Concern

Informed agreement had been acquired from all participant. The study protocol had approved by the local institutional review committee.

Statistical Analysis

Information had analyzed using SPSS program (V-20). Descriptive statistics pertaining to obtained variables had compatibly used. A significance (p-value) less than or equal to 0.05 had considered. Multiple regression analysis had performed when there was a need to minimize the effects of any confounders. ROC curves analysis had applied to evaluate specificity, sensitivity, accuracy and significant use of IL-1B for asthma prediction.

Results

Table-1 shows the characteristics of patients and control groups and the degree of significance between them. There was significant difference between both groups regarding the levels of BMI and FENO test, while no significant difference regarding ages, the levels of IL-1β, waist, hip and waist/hip measurements.

Table 1. Characteristics and outcomes of asthmatic and control subjects and their significance

	BMI	FENO (ppm)	IL-1β	Age	Duration/y	Waist	Hip	Waist/hip
Total mean± SD	29.8±5.4	28.6±28.2	138.2±207.2	34.1±12.7	8.02±8.2	94.7±14.3	105.6±10.6	0.89±.07
Asthma (*N*=127)	30.6±5.5	43.8±29.5	134.8±184.1	33.3±13.0	8.02±8.2	96.1±15	107.1±10.4	0.89±0.08
Control (*N*=60)	28.8±5.1	8.95±4.08	60.4±90.6	34.8±10.4		92.9±13.3	103.8±10.6	0.89±0.06
Significance	0.041	0.001	0.82	0.33		0.18	0.07	0.8

Table-2 shows the degree of significant levels between asthmatic males and females regarding some parameters. The study revealed significant difference regarding waist/hip ratio only between the two sexes.

Table 2. Gender distribution of study parameters and their significance in asthmatic patients

	Age	BMI	Waist/Hip Ratio	FENO	IL-1β	Duration/years
Males	53±12.4	30.9±5.3	0.94±0.06	46.06±34.8	100.6±157.1	8.6±9.8
Females	33.6±13.4	30.7±5.2	0.85±0.07	41.8±24.3	172.3±205.4	7.5±6.9
Significance	0.07	0.6	0.001	0.54	0.12	0.48

The study also revealed no significant correlation between the levels of FENO and IL-1β with body weight as measured by BMI and waist/hip ratio as illustrated in table (3) and figure (1-B), in addition to that no correlation between asthma and body weight as shown in figure (1-A).

Table 3. Correlation (r) and significance (p) of FENO test and IL-1β to Waist/Hip Ratio and BMI in study groups

	Asthmatic Patients (No=127)					Control (No=60)				
	Mean± SD	Waist/Hip		BMI		Mean± SD	Waist/Hip		BMI	
		r	*p*	*r*	*p*		*r*	*p*	*r*	*p*
FENO	43.8±29.5	-0.08	0.45	-0.19	0.09	9.9±4.1	0.11	0.53	-0.17	0.18
IL-1β	134.8±184.1	0.09	0.59	0.19	0.12	60.4±90.6	0.13	0.63	0.28	0.29

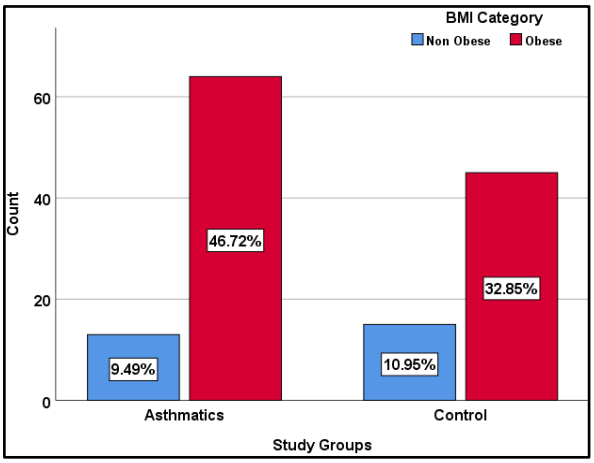


Figure 1A. Comparison between BMI in asthma and control group

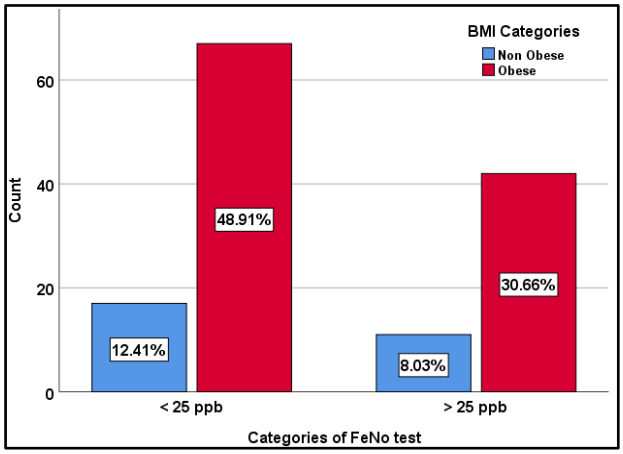


Figure 1B. Relation between FENO and BMI in asthmatic patient

Table (4) illustrate that there was no correlation between duration of asthma with the levels of FENO and IL-1β

Table 4. The correlation between FENO and IL-1β with duration of asthma

	Asthmatic Patients (No=127)		
	Mean±SD	Duration of asthma	
		r	*p*
FENO	43.8±29.5	-0.20	0.08
IL-1β	134.8±184.1	0.09	0.48

ROC curve analysis (figure-2 A and B) of FENO test in BA patients, showed AUC, sensitivity and specificity: 0.967, 92% and 90% at 95% CI [0.941-0.992] which was highly significant (p-0.000). However, ROC curve analysis of IL-1β in BA patients revealed non-significant (p-0.53), and lower accuracy, AUC, sensitivity and specificity: 0.56.4, 62% and 57% with cutoff point of 27.7 at 95% CI [0.42-0.70] to distinguish BA patients from healthy subjects.

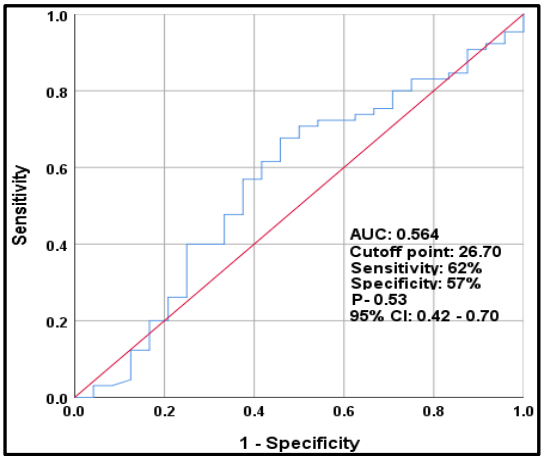


Figure 2A. ROC of Interleukine-1B in Asthmatic Patients

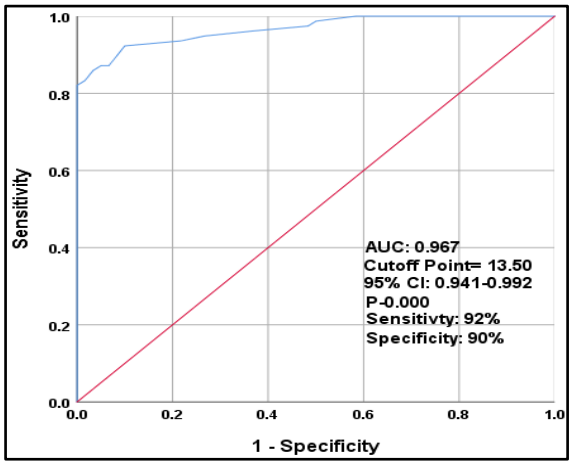
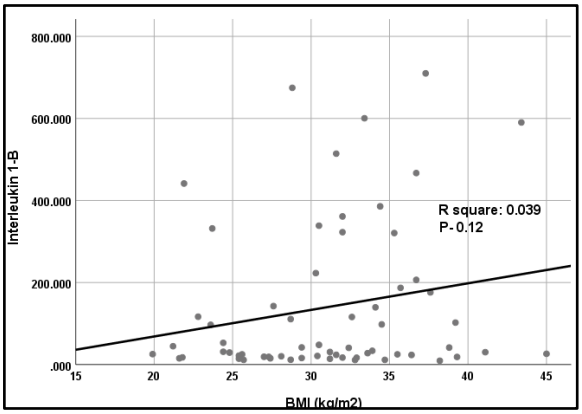


Figure 2B. ROC of FENO in Asthmatic Patient

Figures-3-A and B, revealed non-significant associations of both FENO and BMI with levels of interleukine-1B.



Figures 3A. Correlation between BMI and IL-1B

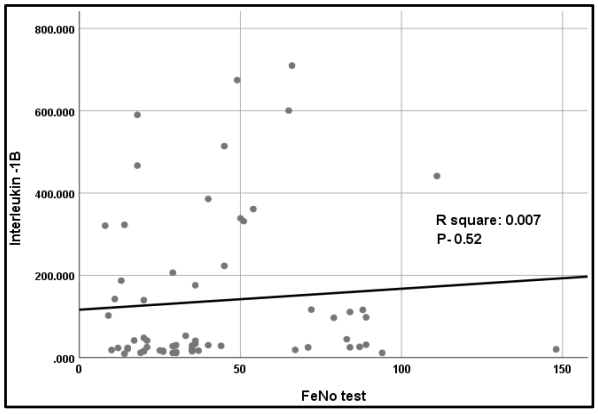


Figure 3B. Correlation between BMI and FENO

Discussion

The FENO had established initially in asthma in the 90s of last century, where there has been a large attention in its possible benefit in asthma management. Thereafter, FENO had verified as an pointer for asthma control, and could mirrors eosinophilic bronchial inflammatory response (Taylor et al., 2008). In this study, the authors measured the level of FENO and IL-1B in asthmatic patients and compared them with subjects without asthma (control group). In comparison to normal individuals, the FENO was raised in asthmatics, and its levels vary with asthma activity and associated to anti-inflammatory treatment.

ROC curves revealed that FENO test had a higher specificity and sensitivity for diagnosing asthma than IL-1β. This FENO finding agrees with our prior study on asthma (Amjed H., 2021).

As a significant health entities globally, both bronchial asthma and obesity are chronic conditions that sharing same risk-factors (Maalej et al., 2012). Therefore, incidence of asthma might

increase with obesity. Some revisions propose that asthma, in obese patients, may have a specific phenotype and contributing to its asthma prognostication.

In our study, though BMI was more elevated in asthmatic patients than control group but there was no important relation between obesity and severity of inflammation as determined by level of FENO. To such a degree, in a study involved 200 asthmatic adults, the authors reported no association of obesity with asthma phenotyping (Pelegrino et al., 2007). Likewise, Lavoie and his group (Lavoie et al., 2006) revealed no association between BMI and asthma severity.

Along the same lines, our results revealed non-significant positive associations of BMI with levels of IL-1 β that had also reported by other studies (Taylor et al., 2008). However, a Japanian study had revealed higher serum levels of IL-1 β in obese compared to non-obese patients (Shoda et al., 2017). Obesity has lately been reported as chronic inflammatory activity, in which the fat tissue has endocrine secretions of pro-inflammatory cytokines like IL-1B (Rho et al., 2009, Amjed H., 2021).

This work revealed non-significant association between asthma and IL-1β level, a subject that still a matter of debates among the researchers. In one asthma study, symptomatic patients show higher IL-1β levels compared to asymptomatic patients (Mahajan and Mehta, 2006). The authors explained such higher levels of IL-1β by both higher expression of IL-1β in the epithelium of asthmatic bronchioles, besides an enhanced expression of IL-1β from macrophages (Pospelova et al., 2013). As well, IL-1β enhances bronchial tree neutrophilia and hyper-responsiveness ''selectively'' to bradykinin (Souza et al., 2019).

Additionally, transforming growth factor-β (TGF-β) is a pleotropic-cytokine (Hayder AA. Al-Hindy, 2020, Fouad SD., 2020, Mazin J. Mousa, 2020, Samer MM., 2020), formed by respiratory epithelial tissue and stimulates fibroblasts growth which may induces fibrotic lung changes (Amjed H., 2021). Previous studies demonstrated an increased TGF-β1 in obstructive pulmonary disease (Judith C.W. Mak, 2009). It had revealed that TGFB and IL-1B modulate T-helper-17 cells that plays a crucial role in the pathophysiology of chronic inflammation (Pourgholaminejad et al., 2016).

Both TGFB and interleukins can induce platelets derived growth factor (PDGF) release (Mehta, 2006, Bash H., 2021). PDGF is a potent mitogen produced by a diversity of cells including fibroblast (Fouad SD., 2020, Hayder AA Maki, 2020, Raghdan Z., 2020) exposed to play an immune-regulatory role in asthma by mediating remodeling of bronchial airways (Kardas et al., 2020).

The non-association between asthma and IL-1β in our study is consistent with a study of Thomas and associates (Thomas and Chhabra, 2003), which could be most patients had increased FENO level is usually associated with eosinophilic asthma that had no much increase in level of IL-1β. The expression of IL-1B enhanced once circulating monocytes exposed to bacterial products (endotoxins). Endotoxin presence can be expected in bronchial passages instead of the blood and hence, the release of IL-1B anticipated more in broncho-alveolar secretions than in blood, though an increased intracellular IL-1B expression in the monocytes can ensue (Whelan et al., 2004).

Conclusion

The study identified no relation between obesity and eosinophilic airways inflammation. The measurement of FENO level is more important in assessment of asthma inflammation than IL-1β.

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