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High-Sensitivity C - reactive protein Assessment in Bronchial Asthma: Impact of Exhaled Nitric Oxide and Body Mass Index

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ABSTRACT

Background: Bronchial asthma (BA), is a chronic airway inflammatory illness affecting over 315 million individuals globally, initiating a major cause for illness and significant burden on communities. C-reactive protein (CRP) is a finely delicate, nonspecific biomarker of acute phase inflammation and injured cells. This protein is raised up during early stages of inflammation in bronchial asthma. The fraction exhaled nitric oxide test is feasible and non-invasive test, also it delivers an immediate result, besides it is reproducible marker of airways inflammation This study designed to illuminate the relationship between Hs/CRP levels, and FeNo index in patients with asthma.

Patients and methods: the study was performed in Merjan Medical City and spiro private clinic, it included 80 asthmatic patients with 60 healthy subjects as control group. The age ranged from 10 to 66 years old, male was dominant. The asthma was assessed using fractional exhaled nitric oxide (FeNo) test (medisoft® company, Belgium)

Results: Mean age of all study participants was 33.3±13.0, the asthmatic patients were on treatment for mean duration of 8.02 years. The mean obesity indices being significantly higher in BA group (p-0.041). Both FeNo and Hs/CRP levels were expressively high in individuals with mean of 28.6±28.2 ppb (p-0.001) and (p-0.028) sequentially. Meanwhile, there was no significant correlation of Hs/CRP with W/H, BMI, and duration of the asthma in BA patients. There was no effect of history of asthma treatment on the blood levels of Hs/CRP (p-0.34). Nevertheless, those on regular asthma therapy correlated with decreased levels of FeNo test (p-0.001). More than 50% of obese patients had higher levels of Hs/CRP. This is not the case for relation of obesity with the two FeNo categories which was not significant. In the meantime, the FeNo levels were significantly increased with the increment of Hs/CRP classes. ROC curve analysis of FeNo test in BA patients, showed significant (p-0.000) high accuracy, AUC, sensitivity and specificity. However, ROC curve analysis of Hs/CRP in BA patients revealed significant (p-0.006), but, lower accuracy, AUC, sensitivity and specificity.

Conclusion: In this study, there was strong correlation between degree of systemic inflammation as assessed by hs-CRP and asthma inflammation as assessed by measuring exhaled nitric oxide (FeNo concentration**).** In addition, there was high correlation between increased body weight with asthmatic airways inflammation

Key wards: Fraction exhaled nitric oxide (FeNo), asthma, high-sensitive C-reactive protein**.**

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INTRODUCTION

Bronchial asthma (BA), is a chronic airway inflammatory illness affecting over 315 million individuals globally, initiating a major cause for illness and significant burden on communities. It still continues to be under-diagnosed and under-treated. Ongoing inflamed airways passages in asthma subsidizes to frail control. C-reactive protein (CRP) is a finely delicate, nonspecific biomarker of acute-phase inflammation (API) and injured cells. Likewise, CRP is raised up during early stages of inflammatory response of chronic obstructive pulmonary disease (COPD) and bronchial asthma (BA) mutually [1, 2].

Both interleukins 1 and 6 adjust high-sensitivity CRP (Hs/CRP) and contribute in airway inflammatory response. Higher Hs/CRP levels are associated with impaired lung function and respiratory hyper-responsiveness. In asthma as API, there is a fast CRP synthesis that act as a universal forager molecule as well as aids in processes of opsonization, phagosis and cell toxicity. Therefore, it is rational to study the presence of relationship between asthma (inflammatory state) and Hs/CRP blood concentrations [3].

In current era, new approaches for evaluation of BA have been established. Of these, using of the fraction exhaled nitric oxide (FeNo) test has payed attention as it is feasible, delivers an immediate result, non-invasive, besides it is reproducible marker of airway inflammation. Numerous works have been directed to authenticate the opportunity of using the FeNo test in BA and respiratory function tests for the management of asthma. There are main progresses in FeNo and its association to inflammatory airways states; still, its aptitude to estimate course of BA leftovers uncertain [4]. For this purpose, our study designed to illuminate the relationship between Hs/CRP levels, FeNo index in patients with asthma.

PATIENTS AND METHODS

The study was performed in Merjan Medical City and Spiro private clinic in Babylon province. it included 80 asthmatic patients with 60 healthy subjects as control group. The age ranged from 10 to 60 years old, male was dominant. The asthma was assessed using fractional exhaled nitric oxide (FeNo) test (medisoft® company, Belgium). FeNo concentrations were 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 tiple measures. Highly sensitive CRP was measured by using HSCRP CALBIOTECH® ELISA kit. 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. Non-obese and obese were delineated as a BMI <25 and ≥25 kg/m^2, respectively [5]. FeNo measures were stratified to "low (<25ppb),

intermediate/high (⩾25ppb) consistent with the ATS recommendations [4]. Cigarette-smokers show increased Hs/CRP levels and cigarette-termination leads to a decreased Hs/CRP concentration. That's why, current smoker participants were excepted from our study.

Statistical analysis

The data were analyzed using SPSS program (version 20). Descriptive statistics pertaining to obtained variables were compatibly used. Levels of Hs/CRP of subjects classified according to the American Heart Association into three quartiles. A one-way ANOVA was used to determine differences among the (quartiles and group) means. A significance (*p*-value) less than or equal to 0.050 was considered. Multiple regression analysis was performed when there was a need to minimize the effects of any confounders. ROC analysis was applied to evaluate specificity, sensitivity, accuracy and significant use of Cy/C and Hs/CRP for asthma prediction.

RESULTS

Mean age of all study participants was 33.3±13.0 years. The asthmatic patients were on treatment for mean duration of 8.02 years. The mean W/H ratio was 0.89±.07, while the BMI was 29.8±5.4; thereby obesity indices being significantly higher in asthmatics (*p*-0.041). FeNo index was significantly higher in asthmatic subject with mean value of 28.6±28.2 ppb (*p*-0.001). In the same way, Hs/CRP measures were significantly (*p*-0.028) high in BA group (tables 1 and 2). The gender show no much significant impact on study parameters other than W/H ratio which significantly (*p*-0.001) more in females (table-3).

Table 1: Mean, standard deviation, minimum and maximum measures of study parameters

	Age	Duration/ys	Weight	Height	BMI	Waist	Hip	W/H	FeNo	HSCRP
Mean	34.1	8.02	80.9	1.64	29.8	94.7	105.6	0.89	28.6	4.6
Std. Deviation	11.9	8.2	15.4	0.17	5.4	14.3	10.6	0.07	28.2	7.72
Minimum	10	1	49	1.5	18	64	78	0.73	2	.01
Maximum	66	40	126	2	45	128	134	1.06	148	89.0

Table 2: Characteristics and outcomes of asthmatic and control subjects and their significance

	Total mean±SD	Groups	Mean±SD	P-Value
BMI	29.8±5.4	1	30.6±5.5	0.041
		2	28.8±5.1	
FeNo	28.6±28.2	1	43.8±29.5	0.001
		2	8.95±4.08	
Hs/CRP	4.6±7.7	1	5.34±8.9	0.028
		2	3.31±3.49	
Age	33.3±13.0	1	33.3±13.0	0.33
		2	34.8±10.4	
Duration/y	8.02±8.2	1	8.02±8.2	
Waist	94.7±14.3	1	96.1±15	0.18
		2	92.9±13.3	
Hip	105.6±10.6	1	107.1±10.4	0.07
		2	103.8±10.6	
Waist/Hip	0.89±.07	1	0.89±0.08	0.8
		2	0.89±0.06	

Table 3: Gender distribution of study parameters and their significance

	Sex	Mean±SD	Significance
Age	M	33.7±11.2	0.6
	F	34.4±12.6	
BMI	M	28.9±5.4	0.057
	F	30.7±5.2	
Waist/Hip Ratio	M	0.93±.05	0.001
	F	0.85±.06	
feNO	M	28.5±31.2	0.9
	F	28.7±25.1	

HSCRP	M	4.5±9.4	0.7
	F	4.8±5.5	
Duration/years	M	8.6±9.8	0.4
	F	7.5±6.9	

There was no significant correlation of both FeNo test and Hs/CRP to W/H ratio and BMI among control groups. Even though in BA patients a negative significant correlation of FeNo with BMI and duration of asthma but not with W/H ratio. Meanwhile, there was no significant correlation of Hs/CRP with W/H, BMI, and duration of the asthma in BA patients (table-4).

Table 4: Correlation of FeNo test and Hs/CRP to Waist/Hip Ratio and BMI in study groups

	Asthmatic Patients (No=127)							Control (No=60)				
	Mean±SD	Waist/Hip		BMI		Duration		Mean±SD	Waist/Hip		BMI	
		r	*p*	*r*	*p*	*r*	*p*		*r*	*p*	*r*	*p*
FeNo	43.8±29.5	-0.08	0.45	-0.19	0.09	-0.20	0.08	9.9±4.1	0.11	0.53	-0.17	0.18
Hs/CRP	5.3±433	0.06	0.55	0.13	0.23	0.07	0.3	3.3±3.4	0.39	0.53	0.26	0.31

Effect of asthma therapy on FeNo and Hs/CRP levels among asthmatic patients is well studied in table-5. It reveals that no effect of history of treatment of BA on the blood levels of Hs/CRP (*p*-0.34). Nevertheless, those on regular asthma therapy obviously correlated with decreased levels of FeNo test (*p*-0.001).

Table 5: Effect of asthma therapy on FeNo and Hs/CRP among asthmatic patients

	Treatment	Mean	Std. Deviation	P-value
Hs/CRP	On treatment	6.3792	11.98	0.34
	With out	4.6778	6.03	
FeNo	On treatment	29.6	19.4	0.001
	With out	49.75	31.1	

Regarding the relation of obesity with Hs/CRP levels, figure-1 exposed that more than 50% of obese patients had higher levels of Hs/CRP.

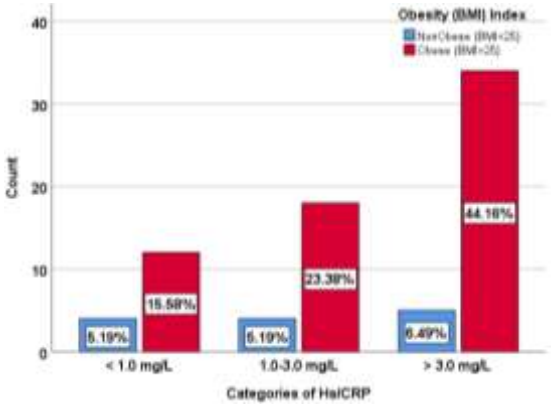

Figure 1: Obesity (No and %) according to the categories of Hs/CRP in asthmatic patients

This is not the case for relation of obesity with the two FeNo categories which was not significant (fig-2). In the meantime, the FeNo levels were significantly increased with the increment of Hs/CRP classes (fig-3).

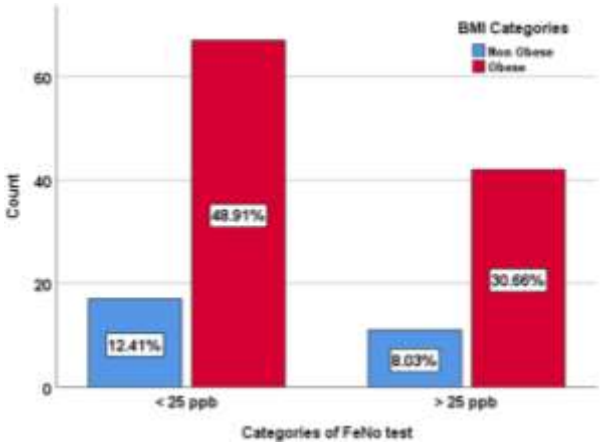

Figure 2: Obesity (No and %) according to the categories of FeNo test in asthmatic patients

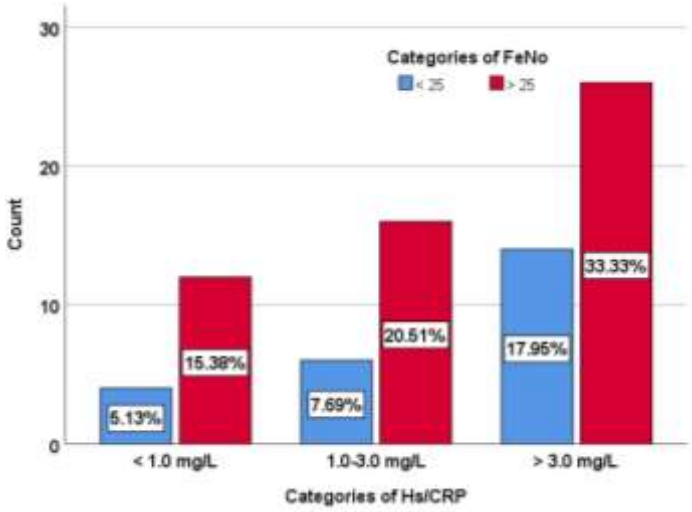

Figure 3: Distribution of FeNo levels according to categories of Hs/CRP

ROC curve analysis (figure-4) of FeNo test in BA patients, showed significant (*p*-0.000) high accuracy, AUC, sensitivity and specificity: 96.7% ,[0.967], [92% and 90%] at 95% CI [0.941-0.992]. However, ROC curve analysis of Hs/CRP in BA patients revealed significant (*p*-0.006), but, lower accuracy, AUC, sensitivity and specificity: 62.6% [0.626, 58% and 41%] and cutoff point of 2.75 at 95% CI [0.53-0.71] to distinguish BA patients from healthy subjects.

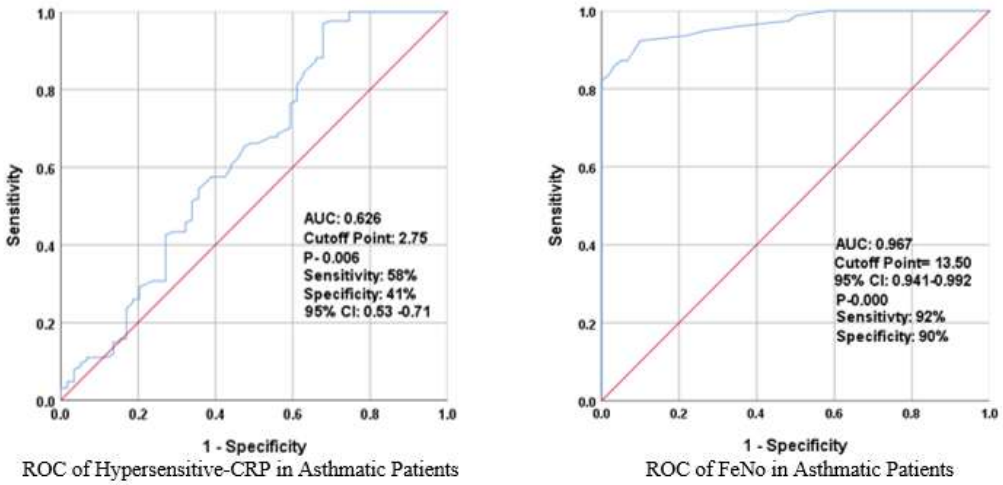

Figure 4: ROC analysis of Hs/CRP and FeNo test in asthmatic patients.

DISCUSSION

In BA, and predominantly in the severe form, various markers were considered, nevertheless, only limited number thus far, can be simply applied in clinical field. Unfortunately, at present, an ideal model doesn't exist and there is an actual-overlay among the biomarkers [6]. In this paper, the discussion centers on the correlation between obesity indices, serum Hs/CRP levels, and FeNo index in BA patients. Hs/CRP levels and FeNo index were significantly higher in BA patients compared to control group.

Obesity indices (HC, WC, W/H ratio and BMI)

Obesity, can be considered as low-grade inflammatory state, has an association with BA, CRP, as acute-phase reacting protein, is raised up in obese individuals, yet little is identified about the actual interaction of asthma with CRP levels [7]. The WHO stated that from 1975 to 2016 the international-obesity-incidence, virtually trebled therefore, by 2016 about 39 percent of adults world-wide labeled as over-weight and 13 percent as obese [8]. The concordant upsurge of both states has raised up theory that the two are causally intercorrelated. In line with a prospective research supports this likelihood [9] and few recent works [7, 10], our results show a significant association between BA and obesity, although in BA patients a negative significant correlation of FeNo with BMI and duration of asthma were present.

Obesity is awfully usual in violent BA. Contemporary ideas about the pathophysiologic background for the effect of overweight in BA including probable effects for vitamin-D deficit, inflammatory response, in addition to the microbiota [11]. The possible effect of vitamin-D is seeming irrelated to impacts on immunomodification, but rather, because of sequestration of vitamin D as a fat-soluble in an adipose tissue [12], which is unlike the outcomes of Martineau *et al.,* which report no role of vitamin-D on aggravations of BA [11]. Obesity can expand adipose tissue as it is a low-grade inflammation, hence increases distance isolating adipocytes and their vessels, causing hypoxic death and recruiting macrophages. Thereafter, the released fatty-acids from unlived adipocytes activate these macrophages that generate inflammatory cytokines, like IL1β, TN-α, and IL6. The cytokines escape to the blood and may thus affect the lungs [13].

Of note, disorders which are obesity-related are regulated by the gut microbiota such as hyperglycemia, insulin-resistance, as well as body inflammation. Likewise, microbiota inhabit lungs which is in addition to gut microbiomes can distress asthma. In severest BA, the pulmonary microbiota varies among obese and normal persons too [11, 14, 15].

Fraction exhaled nitric oxide (FeNo) test

The FeNo level is a marker of activation of inflammatory T2-helper cell in the air-passages. FeNo may emulate features of inflammatory T2-driven cells irrelated directly to eosinophils [4]. In consistent to the underlying arguments [2, 4, 16], our results also infavor higher FeNo levels in untreated compared to treated BA. However, other investigators who exactly studied the relation of FeNo measures with BA control, relied on the "GINA-criteria", showed no statistical variation [2]. The later inconsistency might be justified by variation of participants collection or methodological differences: those who reveal no association between FeNo measures and the BA control included children, while our study included only adults, or source of data collection may be from the caregivers not from the asthmatic patients directly. FeNo concentration test is pertinent in actual circumstances as it is convenient (compared with bronchial biopsy or eosinophil counts); non-traumatic; besides it is confidently associated with other biomarkers of inflammation [17]. That's why, the ATS as well as several other medical societies' acclaims FeNo testing to screen airway inflammation in medical practice [4]. Consistent with other studies, our results reveal no relation between both asthma-duration and BMI with FeNo index [18].

In our study, there was a negative correlation between both age and gender with FeNo levels. Which is not greatly differ from results of other authors, for instance (in one study) FeNo was 25% lower in females and 60% higher in atopic BA [4, 18, 19], nevertheless, other studies reported sex preponderance [19, 20]. The poor correlation results in this work generally might be to some extent ascribed to multiple BA patient factors like diverse endotypes and phenotypes and various control treatments with inhaled steroids and β-agonists bear in mind factors other than inflammation, concomitant illnesses like esophageal reflux and emotional disorders.

Hypersensitive C-reactive protein (Hs/CRP)

It is noteworthy that even though FeNo is a biomarker of eosinophilic inflammation, its usefulness is debatable yet. Hs/CRP is a sensitive biomarker of inflammation, and damaged tissues. In BA, local and systemic inflammation ensue and Hs/CRP may contribute its pathogenicity [20]. Along the same lines, in our study Hs/CRP levels were significantly higher in BA subjects than in control group; as well as a significant correlation between Hs/CRP with FeNo concentrations was described. Supporting this, several other researchers revealed a positive correlation as well [21].

Correlation between Fraction exhaled nitric oxide (FeNo) test and Hypersensitive C-reactive protein

As a rebuttal to this point, it might be (convincingly) argued that FeNo levels not correlated to plasma Hs/CRP in two other works. The first was a retrospective study evaluating stable patients from Pulmonary Department of the Second Clinical College, Jinan University, China [21]; and the second conducted at Louisiana State University Health Sciences Center, USA [22]. An Iranian study directed at Kurdistan University of Medical Sciences, Sanandaj, found no association between grade of systemic inflammation assessed by Hs/CRP with parameters of asthma control [20].

In our study, the duration of BA and BMI were no correlated with blood Hs/CRP values. But then, elevated BMI is associated progressively with raised Hs/CRP

measures even amongst healthy group, that may lead to the belief of a low-grade inflammatory state in obesity [23]. This view is in line with conclusions stated by two other analysis [23, 24]. Our results contradict those of a previously conducted investigates that displayed correlation between the Hs/CRP levels and history of treatment [25, 26]. CRP is a pro-inflammatory factor which enhance many inflammatory-cytokines like interleukins: 1β, 6, 8 and 18 in response to asthmatic inflammation. In contrast, Takemura *et al.,* noticed raised CRP levels in corticosteroid naive BA compared to healthy subject but not in BA on steroids inhaler [24]. While in another analyses, serum CRP values in moderately BA were significantly more than mild asthmatic patients [26]. Other two analyses revealed that non-allergic BA specially has strong association with raised CRP values, although allergic BA is not [27, 28].

The raised CRP values detected in some study participants which were on treatment may be due to undue exposure to some environmental irritants or infectious agent reflecting their influences on the bronchial tree [29]. The genetic bases for biomarkers of systemic inflammation and disposition to an enhanced immune response may be intricated in the correlation between pulmonary indices and CRP [30, 31]. Mostly, high systemic inflammation may be a mirror of a poor over-all wellbeing state, henceforth its relation with pulmonary functions [32]. Greatest surveys recorded that the inflammation in poorly controlled BA patients more than well-controlled BA [33]. Nevertheless, no works have yet been precisely intended to answer these enquiries.

To conclude, the impact of Hs/CRP in assessing BA advances the clinical field along these lines; Hs/CRP is easy to measure, pertinent test, as well as valuable during followup practice. Hs/CRP can be utilized for judging the control of the BA signs, therefore we proposed Hs/CRP as a probable ancillary biomarker of inflammation that can reflect BA severity and control mutually. Therefore, additional extended researches are required to scrutinize such influence.

CONCLUSIONS

In this study, there was strong correlation between Hs/CRP levels (degree of systemic inflammation) and FeNo index (asthma inflammation). In addition, there was high correlation between BMI (increased body weight) with asthmatic airways inflammation.

LIMITATIONS

Few limitations fronting our work; small sample size besides the study was not a longitudinal. The entire asthmatic participants should be assessed for the asthma-control of by using of ACT or ACQF according to GINA guiding-principles. Pulmonary function test should be used also.

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