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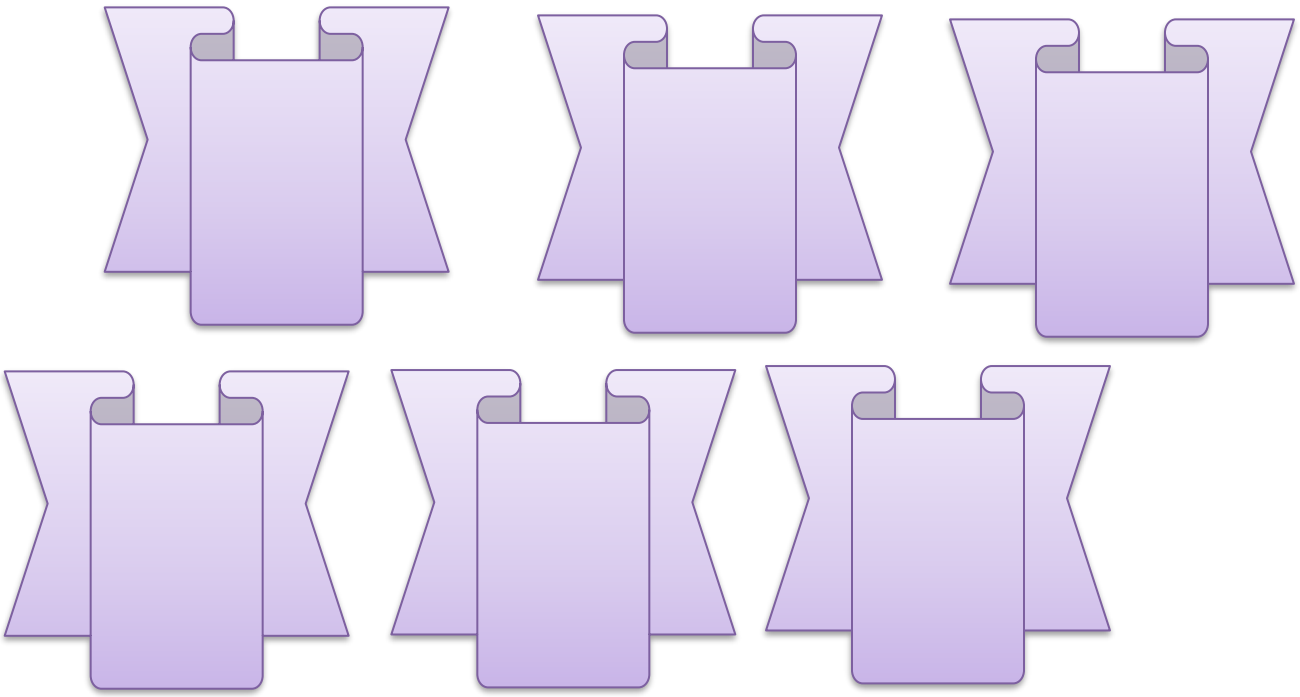

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Original Article

The Role of Serum Myeloperoxidase in Prediction of Severe Bronchial Asthma

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ABSTRACT

Background: Bronchial asthma increasing all over the world and the need of a gold-standard biomarkers for prediction of asthma and follow up of treatment is mandatory. However, it is still not existing.

Aim of the work: To measure the serum level of plasma myeloperoxidase [MPO], and its correlation with respiratory function as well as its predictive power of asthma and its severity.

Patients and Methods: The study recruited 130 patients with asthma, with age and sex-matched other 130 healthy controls. Patients were clinically evaluated; respiratory functions were performed and blood samples were drawn to estimate the serum levels of MPO. In addition, sputum was assessed for cellular content. Asthma severity was determined according to available guidelines and both mild and moderate forms were considered as [non-severe form of asthma]. Receiver operation characteristic [ROC] curve was built to assess the predictive power of MPO.

Results: There was female-sex predominance in the study and control groups [65.4% and 70.0%, respectively]. 15.4% had mild, 35.4% had moderate and 49.2% had severe asthma. MPO levels were significantly higher in the study than the control groups [3310.35±373.39 vs. 1900.32±333.57 pg/ml, respectively]. The serum levels of MPO were positively correlated with asthma severity, all cellular content in BAL and body mass index. However, it was inversely correlated with respiratory function. MPO were significantly higher in severe than non-severe forms [3666.59±736.37 vs. 2964.91±554.47 pg/ml, respectively]. MPO had a good predictive power of asthma and its severe form [the AUC was 0.950 and 0.819 respectively].

Conclusion: Serum levels of MPO can used as a good biomarker for diagnosis of asthma and its severity. But results must be treated with caution, and MPO should be used with a panel of biomarkers till more evidence originated to confirm its role from future studies.

Keywords: Myeloperoxidases; Neutrophils; Bronchial Asthma; Bronchoalveolar Lavage.

INTRODUCTION

Bronchial asthma [BA] affects about 300 million individuals worldwide. It is expected to affect another 100 million by 2025 [1-3].

BA characterized by airway inflammation and hyperresponsiveness. Its pathophysiology includes expression of several biochemical mediators with different roles [e.g., bronchoconstriction, proinflammation, or chemokinetic] [4-6].

Thus, evaluation of airway inflammation could be investigated by assessment of inflammatory cells or the levels of the serum levels of their mediators. Neutrophil cells contribute to the inflammation process and this contribution is well-known. However, its precise role in bronchial asthma is not well known. Neutrophils release an enzyme known as myeloperoxidase [MPO]. It released from the primary azurophilic granules of the neutrophils [7, 8].

It is elevated in both sputum and blood of asthmatic patients, reflecting the neutrophil activity in BA in both adults and children [9-11]. However, its clinical value as a predictor of the development of severe asthma is not well-known.

The current work aimed to measure the serum levels of MPO, as an indicator of neutrophil activity. Then, these values correlated with respiratory function and its ability to predict severe asthma were determined.

PATIENTS AND METHODS

The current work was completed in the department of Chest Diseases [Al-Azhar University Hospital, New Damietta], between January 2020 and December 2022]. It included two groups of subjects [each 130 patients]. One group included asthmatic patients [as the study group] and the other group included age- and sex-matched healthy subjects as a control group.

Inclusion criteria

Confirmed diagnosis of asthma [by clinical history and either bronchodilator responsiveness [>12% and 200 mL improvement in forced expiratory volume in 1 s [FEV1] after 180 µg salbutamol metered-dose inhaler] or airway hyperresponsiveness [AHR] [PC_{20} methacholine < 8 mg/mL].

Exclusion criteria

Current smokers or patients received systemic corticosteroids [CS] for ≥ one month before inclusion in the study.

Sampling

Blood samples were drawn by venipuncture of the antecubital or any other suitable vein. All samples collected on capillary tubes, centrifuged at 5000 g/min for 15 minutes after coagulation. Eppendorf tubes were used for collection and storage of the serum. Samples were stored at -20 °C till the time of analysis.

Determination of serum myeloperoxidase

The MPO enzyme was measured in the serum samples by MPO, ELISA Kit. Kits were supplied by [Cloud-Clone Corp.®, USA]. The detection of the Kits extends from 78 to 5500 pg/ml.

Total and differential cell counts in BAL

The BAL was collected and saved as pellets, which were resuspended in 200 mL of phosphate buffer solution [PBS]. Hemocytometer was used for cell count by using 50 µl of cell suspension. Another 50 ml of suspension was further subjected to cytospin at 450 rpm for 5 min, followed by Diff-Quick staining to detect the inflammatory cells. A total of 300 cells were counted under microscopic examination. Cells were counted on the basis of its morphological and staining characteristics. These were eosinophils, neutrophils, macrophages or lymphocytes.

Forced spirometry

It was performed according to American Thoracic Society/European Respiratory Society [ERS/ATS] standards [12].

Statistical analysis

The collected data were anonymized and collected in a tabular form. Then transferred to a personal computer and entered to the statistical package for social sciences, for windows, version 22 [IBM®SPSS®, Chicago, Armonk, USA]. The quantitative data were expressed by their mean and standard deviations, while qualitative data were summarized by their frequency and percentages. Groups were compared by

independent samples student "t" test for quantitative variables and by Chi square for qualitative variables. Pearson's correlation coefficient [r] was calculated to determine bivariate correlations between two variables. The receiver operation characteristic [ROC] curve was used to estimate the predictive ability of MPO for severe asthma. Values of area under the curve [AUC] above 0.7 indicate good predictive power. The p value < 0.05 indicates significant results.

RESULTS

In the current work, there was female-sex predominance in the study and control groups [65.4% and 70.0%, respectively] with no significant differences between study and control groups. In the study group, 15.4% of patients had mild asthma, 35.4% had moderate asthma and 49.2% had severe asthma [table 1].

The results of the current work revealed that, there was no significant differences between the study and the control groups regarding age, weight, height or body mass index [BMI]. However, respiratory functions were significantly reduced and cellular content of the BAL were significantly increased in asthmatic than the control group. Finally, MPO levels were significantly higher in the study than the control groups [3310.35±373.39 vs. 1900.32±333.57 pg/ml, respectively] [table 2].

The serum levels of MPO were significantly and proportionately correlated with asthma severity score, all cellular content in BAL and body mass index. However, the correlation with BMI was mild. In addition, MPO inversely and significantly correlated with measures of respiratory function [table 3].

When we categorized asthma severity into severe and non-severe [included mild and moderate asthma], the levels of MPO still significantly higher in severe than non-severe forms [3666.59±736.37 vs. 2964.91±554.47 pg/ml, respectively] [table 4].

To detect predictive power of MPO for asthma and severe asthma, the ROC curve was used and revealed a good predictive power of MPO for diagnosis of asthma and severe form of asthma. For prediction of asthma, the AUC was 0.950, with sensitivity of 84.62% and specificity of 100.0%. In prediction of severe form of asthma, the AUC was 0.819 with sensitivity of 85.94% and specificity of 86.36% at the MPO values > 3400 pg/ml [table 5 and figures 1 and 2].

Table [1]: Comparison between study and control groups regarding categorical data

		Control [n=130]		Study [n=130]		Test	p
		No.	%	No.	%		
Gender	Male	45	34.6%	39	30.0%	0.63	0.42
	Female	85	65.4%	91	70.0%		
Asthma severity	Mild	-	-	20	15.4%	-	-
	Moderate	-	-	46	35.4%	-	-
	Severe	-	-	64	49.2%	-	-

Table [2]: Comparison between study and control groups regarding quantitative data

	Control [n=130]		Study [n=130]		Test	p
	Mean	SD	Mean	SD		
Age [year]	51.15	6.72	51.98	5.66	1.09	0.28
Weight [kg]	76.14	10.77	78.22	12.12	1.47	0.14
Height [m]	1.67	0.03	1.67	0.03	0.29	0.77
BMI [kg/m^2]	27.35	3.88	28.05	4.32	1.38	0.17
FVC % of predicted	122.14	6.18	105.91	3.45	29.36	**<0.001***
FEV1 % of predicted	95.29	2.45	55.07	10.58	42.2	**<0.001***
FEV1/FVC	0.78	0.04	0.52	0.10	27.40	**<0.001***
Myeloperoxidase [pg/ml]	1900.32	333.57	3310.35	737.39	19.86	**<0.001***
BAL Total Cells [x 10^4]	14.02	4.62	33.76	8.19	23.92	**<0.001***
BAL Eosinophil %	7.11	2.45	16.30	3.75	23.30	**<0.001***
BAL Neutrophil %	12.35	2.51	22.08	4.63	21.04	**<0.001***

*: significant

Table [3]: Correlation between Myeloperoxidase and other variables

	Myeloperoxidase [pg/ml]	
	r	**p**
Asthma severity	0.467	**<0.001***
BAL Total Cells [x 10^4]	0.745	**<0.001***
BAL Eosinophil %	0.747	**<0.001***
BAL Neutrophil %	0.740	**<0.001***
Age [years]	0.076	0.220
BMI [kg/m^2]	0.147	**0.018***
FVC % of predicted	-0.673	**<0.001***
FEV1 % of predicted	-0.818	**<0.001***
FEV1/FVC	-0.790	**<0.001***

Table [4]: Comparison between severe and non-severe asthma as regards serum myeloperoxidase

	Mean	S. D	Minimum	Maximum	t	p
Severe	3666.59	736.37	1350.00	4990.00		
Not severe	2964.91	554.47	1520.00	4999.00	6.14	**<0.001***
Total	3310.35	737.39	1350.00	4999.00		

Table [5]: Area under the ROC curve [AUC] for myeloperoxidase prediction of severe asthma

	Prediction of asthma	Prediction of severe asthma
Area under the ROC curve [AUC]	0.950	0.819
Standard Error	0.0157	0.0438
95% Confidence interval	0.916-0.973	0.742 to 0.881
z statistic	28.613	7.295
Significance level P [Area=0.5]	**<0.0001**	**<0.0001**
Associated criterion [Cutoff]	> 2600	>3400
Sensitivity	84.62	85.94
Specificity	100.00	86.36

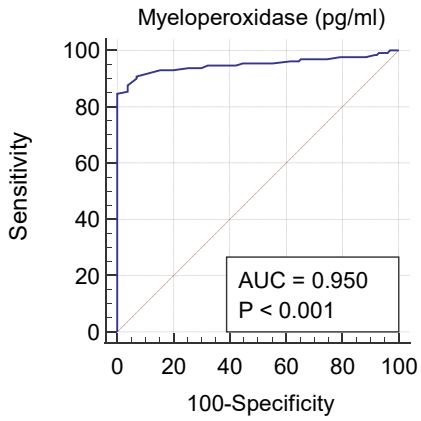

Figure [1]: ROC curve for prediction of asthma

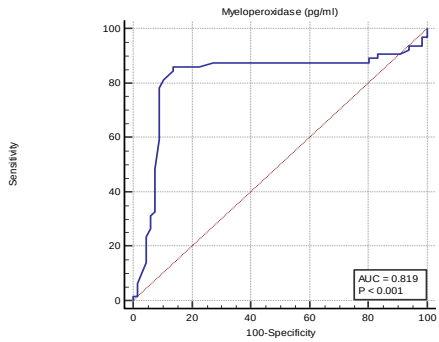

Figure [2]: ROC curve for prediction of severe asthma

DISCUSSION

Serum MPO was significantly increased with asthma than control groups. In addition, it significantly correlated with respiratory function. When ROC curve constructed to test the predictive power of MPO for asthma and its severe form, it showed a good predictive power [for prediction of asthma, the AUC was 0.950, with sensitivity of 84.62% and specificity of 100.0%]. For sever form of asthma, the AUC was 0.819, with sensitivity of 85.94% and specificity of 86.36% at the MPO values > 3400 pg/ml. These results are in accordance with **Aldhalmi *et al.*** [13] who reported significant increase of MPO in asthmatic than healthy controls [3222.5 ± 1280.8 vs. 1670.8 ± 991.6; p value < 0.001]. In addition, they reported a sensitivity of 86.2% and specificity of 86.3% for prediction of asthma. However, the same authors did not find significant differences in the distribution of MPO levels according to asthma levels [mild, moderate and severe forms]. This could be explained by their lower number of included subjects than the current one and abnormal distribution of the MPO levels.

Results of the current work also in line with a previous two trials, that reported significant elevation of serum or sputum levels of MPO in asthma than healthy controls. These results reflecting the neutrophilic effects in asthma and in severe form of asthma [9, 14].

Obaid Abdullah *et al.* [15] reported that, the mean patients' age was 31.9±15.1 year, with a predominance of females, as in the current work. Mean spirometric parameters were significantly lower among patients than controls [p < 0.001]. MPO was significantly higher among BAs than controls [3222.5±1280.8 vs. 1670.8±991.6; p < 0.001]. However, values of MPO levels have not differed significantly with asthma levels of severity, and correlation with respiratory function was statistically non-significant. ROC curves revealed a sensitivity, specificity and accuracy for MPO [80.9%, 72.1%, and 84.3%], respectively to predict asthmatic severity, indicating good prediction as in the current work.

Wang *et al.* [16] also reported meaningful variance of MPO levels in asthmatics throughout attacks, but not in asthmatic patients in remission, indicating a role of MPO in pathogenesis and exacerbations of asthma. Also, previous studies recommended that, neutrophils and/or MPO are not the main pathogenic players of asthma inflammation [17, 18]; thus, other roles are suspected. Higher levels of MPO in adult patients with asthma may be related to associated infection, as neutrophil activation defends the body against bacterial invasion. A well-known fact that infections exacerbates the bronchial asthma and this confirm the results of the previous work of **Wang *et al.*** [16].

As the prevalence of bronchial asthma increases all over the world in the last decades, the existence for a gold-standard biomarker is increasingly required. However, and un-fortunately, this biomarker is not existing. MPO [according to the results of the current work] seems to be a promising biomarker. However, the current work has some limitations [small number of the included subjects and absence of other biomarkers for comparison]. Besides the contradictory results of the predictive power of MPO reported in previous studies, MPO could not be treated as the golden biomarker in patients with bronchial asthma or its severity. Future studies are recommended. However, it may be included with a panel of biomarkers at the current moment till the emergence of new evidence.

Conflict of Interest and Financial Disclosure: None.

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