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Original Article

The Role of Sputum Clusterin in Childhood Asthma in Zagazig University Hospitals

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ABSTRACT

Clusterin serves as a highly sensitive cellular detector for oxidative stress and has been extensively investigated as a significant indicator for disorders related to inflammation. The evaluation of clusterin in pediatric population diagnosed with asthma has not been fully evaluated. **Methods:** This is a case-control study. It was a prospective study carried on Pulmonology unit Pediatric department, Zagazig University hospitals including 54 Patients 7 – 14 years in age, both genders were included, this study was planned to include fifty four (54) subjects; thirty six (36) asthmatic children as patients and another eighteen (18) non asthmatic children as controls.The studied groups underwent the following procedures: history taking ,clinical examination ,Assessment of pulmonary function which included measuring FEV1, FVC, and FEV1/FVC ratio .complete blood count with differential count for eosinophils , total IgE assay, sputum cytology, and An enzyme-linked immunosorbent assay was used to evaluate the clusterin levels in sputum.**Results:** In the current research we had reported that there was a statistically significant difference between studied groups regarding sputum clusterin (p value of ≤0.001) as children diagnosed with controlled asthma had elevated levels of clusterin compared to the control group [14.82(13.74–16.59) ng/mL vs 11.75 (10.82-12.54) ng/mL]. During asthma exacerbation, the levels of clusterin in sputum were decreased compared to controlled asthma [8.13 (4.31–9.41) ng/mL vs 14.82 (13.74–16.59) ng/mL]. Our study reported a statistically significant correlation between the severity of asthma and serum Clusterin in severe asthma as patients with severe asthma had elevated levels of clusterin in comparison to those who had mild asthma [16.47 (15.76–18.12) ng/mL vs 13.79 (12.85-14.03) ng/mL]. **Conclusion**: The total amounts of Clusterin detected in the sputum have changed in patients with both controlled asthma and asthma exacerbation due to its antioxidant and anti-inflammatory properties. Clusterin levels detected in sputum can be considered as a biomarker of airways inflammation and the intensity of symptoms, making it a valuable tool for evaluating childhood asthma.

Keywords: Clusterin, Asthma, Childhood, Pediatric, Severity.

INTRODUCTION

Asthma is a diverse condition, typically marked by persistent inflammation of the airways. The condition is characterized by a fluctuating and varying severity of respiratory symptoms, including wheezing, shortness of breath, chest tightness, and cough, along with intermittent restriction of airflow during exhalation. Airflow restriction may eventually become chronic. Asthma is commonly linked to increased sensitivity and inflammation of the airways, although these factors alone are not enough to confirm the diagnosis according to Global Initiative for Asthma guidelines [1].

The diverse nature of this medical condition is currently being investigated at the molecular and cellular levels, presenting novel possibilities for its prevention and management [2] [3].

Oxidative stress, characterized by a disparity between heightened exposure to reactive oxygen species and the body's ability to defend against them, plays a role in the pathological process of asthma [4].

In asthma, reactive oxygen species are generated internally through various metabolic reactions [5] [6] and externally through environmental factors such as air pollution and smoking [7] [8].

The occurrence of elevated oxidative stress levels can mainly contribute to emergence of asthma which will be refractory and severe [9]. Clusterin is found to be a glycoprotein which is present in various forms of epithelial cells. It is classified as chaperone protein [10] which is considered as a biomarker in response to stress [11]. Clusterin is primarily susceptible to radiation, elevated temperatures and oxidative stress [12].

Asthma biomarkers can be detected in several biological samples, such as urine or blood, bronchoalveolar lavage (BAL), sputum, bronchial biopsy and exhaled breath condensate (EBC) [13].

Clusterin is a glycoprotein which is composed of 2 different chains (chain a and chain b), these chains are joined by five disulphide linkages. It consists of 449 amino acids with a molecular weight around 80 kDa [14].

It is found in the majority of organs of the body, as well as various physiological fluids such as plasma, urine, breast milk, cerebrospinal fluid and semen. Additionally, it is present in certain cell types in nearly all forms of mammalian tissue [15].

For instance, it is present in epithelial cells which are located in the boundaries of tissues and fluids, some subgroups of acinar cells of pancreas and neurons. Additionally, it builds up in the arterial wall as atherosclerosis progresses -16]. Extracellular clusterin production is enhanced in response to various disruptions, such as hypoxia, stress, cell death, or injury. It serves as a versatile cell protector that captures harmful substances during tissue remodeling and degeneration, facilitating their elimination [17].

The association between asthma and this particular topic has not yet been thoroughly investigated. The study conducted by Kwon et al. in 2009 [18] was the first to establish a connection between clusterin and oxidative stress in individuals with asthma. Oxidative stress is a fundamental characteristic in the development of asthma, as highlighted by Bowler and Crapo in 2002 [19]. Hence, clusterin likely plays a role in the process of airway inflammation. The objective of this study was to evaluate the association between levels of clusterin in sputum and pediatric asthma, as well as to examine the correlation between sputum clusterin levels and severity of airway inflammation and pulmonary function.

METHODS

This is a case-control study that was conducted in Pulmonology unit of Pediatric Department and Microbiology Department of Zagazig University Hospitals. This study was planned to include fifty four (54) subjects; thirty six (36) asthmatic children as patients and another eighteen(18) non asthmatic children as controls. The first group included asthmatic children attending asthma outpatient clinic and those admitted in pulmonology ward as cases and the second group includes non-asthmatic, age and sex matched children attending general outpatient clinic or admitted in pediatric University hospital for other causes as a control group. Furthermore, those asthmatic children were further classified into two groups controlled asthma and asthma exacerbation.

controlled asthma sub-classified into two subgroups mild controlled asthma, and moderate to severe controlled asthma. Study groups: Group (A): 18 non asthmatic controls, Group (B1): 9 mild controlled

asthma, Group (B2):9 moderate to severe controlled asthma, Group (C):18 asthma exacerbation.

Inclusion Criteria: All asthmatic children diagnosed newly clinically and by spirometry. Their age were from 7 to 14 years. Both genders were included. Children with recurrent attacks of wheezy chest with positive family history of asthma. Known cases of asthma with or without previous hospital admission.

Exclusion Criteria: We have eliminated children under the age of 7 from our study if their spirometric evaluation cannot be assessed. Patients who had pulmonary diseases other than asthma, cardiovascular diseases requiring daily medication, central nervous system disorders, hepatic disorders, renal disorders, endocrinal disorders, recent use of systemic steroids within the past two weeks, primary or secondary immunodeficiency, lower respiratory tract infection within the past two months, or were taking beta-blocker medication or unable to complete study procedures were excluded.

The study groups underwent the following procedures: Comprehensive collection of medical background information, thorough evaluation of physical condition, and Assessment of pulmonary function which included measuring FEV1, FVC, and FEV1/FVC ratio .complete blood count with differential count for eosinophils , total IgE assay, sputum cytology, and An enzyme-linked immunosorbent assay was used to evaluate the clusterin levels in sputum.

Collection of samples:

The studied participants were directed to rinse their lips with water and then inhale a nebulized 3% saline solution at room temperature using a nebulizer. The children were instructed to cough deeply every 3 minutes thereafter. The sputum samples were stored at a temperature of 4°C for a maximum of 2 hours before being subjected to additional processing. A fraction of the samples were mixed with a phosphate-buffered saline (PBS) solution that had a concentration of 10 mmol/L of dithiothreitol. The mixture was then gently stirred at room temperature for 20 minutes to determine the cell count. The cell pellet was resuspended in PBS after being centrifuged at 400 g for 10 minutes. We employed trypan blue exclusion as a means to verify sufficient viability. Cell counts were conducted using a hemocytometer, and slides were produced and stained with May—Giemsa stain for differential cell count. Airway eosinophilia is characterized by an eosinophil level that is equal to or greater than 3% of the total cell count. The liquid portion was subsequently frozen at -70°C for the later analysis of clusterin.

Sputum clusterin levels were measured using a commercially available enzyme-linked immunosorbent assay kits Sunred human clusterin (clu) ELISA kit 2019 (Baoshan ,Shanghain ,China) according to the manufacturer's instructions.

Statistical analysis: Data obtained from historical records, clinical examinations, laboratory tests, and outcome assessments were organized, inputted, and analyzed using Microsoft Excel software. The data were analyzed using the Statistical Package for the Social Sciences (SPSS), software version 24.0 (SPSS Inc., 2016).

RESULTS

There is no statistically significant difference between the studied groups in terms of gender or age. There is no statistically significant difference between the groups being tested in terms of total IgE or white blood cells. There is a statistically significant difference observed between the groups being evaluated in terms of serum eosinophils. When conducting a post hoc test, there is a substantial difference between group A (the control group) and each of the other groups.

There is a statistically significant difference in FEV1 between the groups that were analyzed. When conducting a post hoc test, there is a substantial difference between group C and every other group. A statistically significant difference exists between the studied groups in terms of FEV1/FVC. When conducting a post hoc test, there is a substantial difference between each pair of groups.

There is a statistically significant difference observed among the tested groups in terms of sputum total leukocyte count (TLC), neutrophil count, and lymphocyte count. When conducting pairwise comparisons, there is a substantial difference between group A (the control group) and each of the other groups. There is a statistically significant difference between the groups under study in terms of sputum eosinophils. When conducting pairwise comparisons, a substantial difference is observed between group A (the control group) and each of the other groups.

There is no statistically significant difference between the groups being researched in terms of their use of ICS(inhaled corticosteroids). There is a statistically significant difference between the analyzed groups in terms of the utilization of systemic steroids and the occurrence of wheezing. Within the controlled asthma and asthma with exacerbation groups, approximately 28% and 61% respectively utilized steroid medication. Wheezes were seen in all individuals experiencing exacerbation of asthma, while only 50% of those with controlled asthma exhibited wheezes .There is a statistically significant variation in sputum clusterin levels between the groups being investigated. When conducting pairwise comparison, there is a significant difference between each pair of groups (p value of ≤0.001) as children diagnosed with controlled asthma had elevated levels of clusterin compared to the control group [14.82(13.74–16.59) ng/mL vs 11.75 (10.82-12.54) ng/mL]. During asthma exacerbation, the levels of clusterin in sputum were decreased compared to controlled asthma [8.13 (4.31–9.41) ng/mL vs 14.82 (13.74–16.59) ng/mL].

The optimal threshold for sputum Clusterin in predicting controlled asthma is ≥13.3. This threshold has an area under the curve of 0.935, a sensitivity of 88.9%, a specificity of 88.9%, a positive predictive value of 88.9%, a negative predictive value of 88.9%, and an overall accuracy of 88.9% (p<0.001).The optimal threshold for sputum Clusterin in predicting asthma exacerbation is ≤10.45. This threshold has an area under the curve of 0.985, a sensitivity of 94.4%, a specificity of 91.7%, a positive predictive value of 85%, a negative predictive value of 97.1%, and an overall accuracy of 92.6%.There is a statistically significant positive connection between the levels of clusterin in sputum and both FEV1 (forced expiratory volume in one second) and FEV1/FVC (ratio of FEV1 to forced vital capacity). A statistically significant negative connection exists between clusterin and sputum eosinophils. There is an insignificant association between it and other indicators.

There is no statistically significant positive connection between sputum clusterin and clinical or laboratory markers in groups of individuals with controlled asthma or those experiencing an exacerbation.

There is a statistically significant correlation between the severity of controlled asthma and the levels of sputum Clusterin, which are much greater in cases of severe asthma as patients with severe asthma had elevated levels of clusterin in comparison to those who had mild asthma [16.47 (15.76–18.12) ng/mL vs 13.79 (12.85-14.03) ng/mL]

Table (1) Comparison between the studied groups regarding demographic data

	Group A	**Group B**	**Group C**	χ^2	**p**
	N=18 (%)	**N=18 (%)**	**N=18 (%)**		
Gender: Female Male	 7 (38.9%) 11 (61.1%)	 7 (38.9%) 11 (61.1%)	 5 (27.8%) 13 (72.2%)	0.478	0.489
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	F	p
Age (year)	9.11 ± 1.91	8.56 ± 1.54	9.89 ± 2.3	2.145	0.128

χ^2 Chi square test F One way ANOVA test

Table (2) Comparison between the studied groups regarding laboratory data

	Group A	**Group B**	**Group C**	**F**	**p**
	N=18 (%)	**N=18 (%)**	**N=18 (%)**		
WBCs ($10^3/mm^3$)	6.79 ± 1.68	6.66 ± 1.48	6.59 ± 2.08	0.058	0.944
Eosinophil ($10^2/mm^3$)	3.08 ± 1.1	5.32 ± 2.48	6.35 ± 2.04	13.051	<0.001**
Tukey HSD	P_1 0.004*	P_2 0.261	P_3 <0.001**		
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**KW**	**p**
Total IgE	17.27 (13.01 –32.62)	20.46 (14.97–56.02)	41.76(18.11–112.23)	5.197	0.074

F One way ANOVA test KW Kruskal Wallis test HSD Highest significant difference *p<0.05 is statistically significant **p≤0.001 is statistically highly significant p1 difference between group A and B p2 difference between groups B and C p3 difference between groups A and C IQR interquartile range

Table (3) Comparison between the studied groups regarding spirometric data

	Group A	**Group B**	**Group C**	**F**	**p**
	N=18 (%)	**N=18 (%)**	**N=18 (%)**		
FEV1 (%)	83.56 ± 3.35	80.67 ± 3.65	64.11 ± 5.23	114.551	<0.001**
Tukey HSD	P_1 0.103	P_2 <0.001**	P_3 <0.001**		
FEV1/FVC	84.5 ± 2.92	74.83 ± 2.81	66.44 ± 8.56	79.435	<0.001**
Tukey HSD	P_1 <0.001**	P_2 <0.001**	P_3 <0.001**		

F One way ANOVA test HSD Highest significant difference *p<0.05 is statistically significant **p≤0.001 is statistically highly significant p1 difference between group A and B p2 difference between groups B and C p3 difference between groups A and C

Table (4) Comparison between the studied groups regarding result of sputum cytology analysis

	Group A	**Group B**	**Group C**	**KW**	**p**
	Median (IQR)	**Median (IQR)**	**Median (IQR)**		
total lekocytic count(TLC)	95(55 – 150)	300(195 – 625)	400(200 – 1025)	25.518	<0.001**
Pairwise	P_1 <0.001**	P_2 0.552	P_3 <0.001**		
Neutrophil (%)	48(23.25 –89.25)	140(67.5–221.25)	164(60 – 425)	12.219	0.002*
Pairwise	P_1 0.007*	P_2 0.581	P_3 0.001**		
Eosinophil (%)	0(0 – 6.25)	5(0 – 23.5)	35(8.75 – 120)	14.139	<0.001**
Pairwise	P_1 0.197	P_2 0.016*	P_3 <0.001**		
Lymphocytes (%)	33.5 (14.75 – 63)	196 (102.5 – 279.75)	157 (116.25–285)	29.157	<0.001**
Pairwise	P_1 <0.001**	P_2 0.84	P_3 <0.001**		

KW Kruskal Wallis test HSD Highest significant difference *p<0.05 is statistically significant **p≤0.001 is statistically highly significant p1 difference between group A and B p2 difference between groups B and C p3 difference between groups A and C IQR interquartile range

Table (5) Comparison between the studied groups regarding disease-specific data

	Group B	**Group C**	χ^2	**p**
	N=18 (%)	**N=18 (%)**		
Systemic Steroid use:				
Absent	13 (72.2%)	7 (38.9%)	4.05	0.044*
Present	5 (27.8%)	11 (61.1%)		
ICS(inhaled steroids)				
Absent	9 (50%)	10 (55.6%)	0.112	0.738
Present	9 (50%)	8 (44.4%)		
Wheezes				
Absent	9 (50%)	0 (0%)	12	0.001**
Present	9 (50%)	18 (100%)		

χ^2Chi square test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table (6) Comparison between the studied groups regarding sputum clusterin (ng/ml)

	Group A (n=18) Median (IQR)	Group B (n=18) Median (IQR)	Group C (n=18) Median (IQR)	KW	p
sputum clusterin	11.75(10.82-12.54)	14.82(13.74–16.59)	8.13(4.31–9.41)	42.638	<0.001**
Pairwise	P1 0.002*	P2 <0.001**	P3 <0.001**		

KW Kruskal Wallis test p1 difference between groups A and B p2 difference between groups C and B p3 difference between groups A and C **p≤0.001 is statistically highly significant *p<0.05 is statistically significant

Table (7) Performance of sputum clusterin in prediction of controlled asthma

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
≥13.3	0.935	88.9%	88.9%	88.9%	88.9%	88.9%	<0.001**

AUC area under curve PPV positive predictive value NPV negative predictive value **p≤0.001 is statistically highly significant

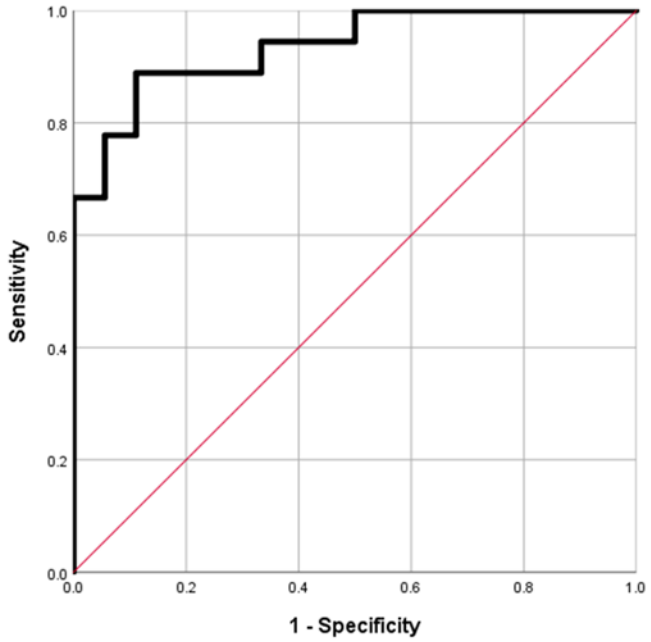

Figure (1) ROC curve showing performance of sputum clusterin in prediction of asthma

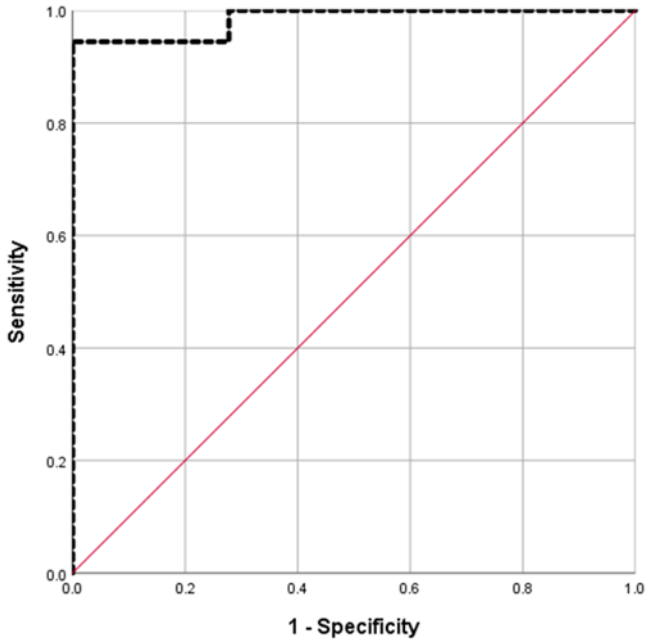

Figure (2) ROC curve showing performance of sputum clusterin in prediction of asthma with exacerbation

DISCUSSION

Asthma is a diverse condition marked by sudden and recurring worsening episodes, occurring alongside long-term inflammation and structural alterations that can lead to ongoing symptoms and reduced lung function [1].

Evaluating the severity and level of control of asthma has been the primary focus in managing the condition. The adjustment of asthma medication has primarily been based on symptoms and lung function [20].

Certain biomarkers can be utilized to monitor the progression of the disease, determine the most effective therapy, and serve as predictors for the risk of exacerbation and long-term consequences [21].

Clusterin is a glycoprotein composed of two different chains, a and b, which are linked together by five disulphide linkages. It consists of 449 amino acids and has a molecular weight of around 80 kDa [14].

The production of clusterin outside of cells is enhanced in response to various disruptions, such as hypoxia, stress, cell death, or injury. Clusterin serves as a versatile cell defender by capturing hazardous substances during tissue remodeling and degeneration, facilitating their elimination [17].

Multiple studies have established a correlation between clusterin and various inflammatory conditions. Therefore, it has been directly linked to the intensity of asthmatic symptoms in children [25].

The primary aim of this study was to investigate the levels of clusterin in sputum samples from children diagnosed with asthma, in comparison to a control group. Additionally, the study aimed to examine the associations between clusterin levels in sputum and markers of airway inflammation, pulmonary function, and the severity of asthma.

This study was planned to include fifty four (54) subjects; thirty six (36) asthmatic children as patients and another eighteen (18) healthy children as controls.

The first group included non-asthmatic children as control the second group included asthmatic children, Furthermore, those asthmatic children were further classified into two

groups controlled asthma and asthma exacerbation

Our data revealed that studied groups; control, stable asthma, asthma exacerbation are closely matched regarding their age and gender where no statistically significant difference between studied groups was found. The current data revealed no significant effect of the age or the sex of patients on their asthma severity.

Conversely, Borrel et al. found a correlation between being male and having inadequate management of asthma, particularly before reaching puberty. This was partially attributable to higher body mass index (BMI) among the boys in the study [27].

These differences may be related to different populations studied with ethnic varieties and different compliance and availability of asthma medications.

Regarding peripheral eosinophils count Our study revealed the presence of highly significant differences between asthmatic children and the control group with increased levels of peripheral eosinophils count among asthmatic children (controlled asthma and exacerbation) (***p*** value of ≤0.001).

Eosinophils play a role in the pathophysiology of different diseases, such as parasitic and allergic diseases. Eosinophils migrate from the bloodstream to sites of inflammation, where they exert several activities by directly regulating cytokines and inflammatory responses. Additionally, they serve as antigen-presenting cells during inflammatory reactions [27].

Blood eosinophils are valuable for identifying individuals with asthma who will have a positive response to biological therapies, such as anti-IL-5 [28].

The findings of our study showed no statistically significant difference between the asthmatic children and the control group in terms of total IgE or white blood cells.

The clinical significance of total IgE as a biomarker for allergic or eosinophilic asthma remains uncertain. So far, both baseline total and specific IgE have not shown the ability to predict how well biologic treatment will work for allergic or eosinophilic diseases. Therefore, the main use of IgE in clinical practice is currently to help determine the appropriate dosage of omalizumab, even though it does not actually predict how likely the treatment will be effective [15].

IgE levels have been crucial in assessing individuals with allergic diseases for a significant period of time, although there have been reports of inadequate sensitivity [15].

Our study showed significant difference between asthmatic patients and controls regarding FEV1 and FEV1/FVC (***p*** value of ≤0.001).

When diagnosing asthma, symptoms, clinical findings, and responsiveness to asthma drugs are all significant approaches. However, spirometry is considered the more objective method for diagnosing asthma **[29].**

In comparison to the controls, the patients with controlled asthma exhibited a reduced percentage of FEV1, FEV1/forced vital capacity (FVC), and forced expiratory flow at 25–75% of vital capacity (FEF25–75%), which indicates the presence of airway blockage [22].

The results of our study showed a notable difference in sputum eosinophils between children with asthma and those without asthma, with a p-value of ≤0.001.The sputum eosinophil count is increased in individuals with controlled asthma and far more increased after asthma exacerbation. When possible, analyzing sputum can offer additional insights on the cellular makeup and cytokines present in the airway. Elevated eosinophil count in sputum is a characteristic sign of atopy and asthma [30].

In our study, there is no statistically significant difference between the controlled asthma group and the group experiencing asthma exacerbation in terms of the use of inhaled corticosteroids (ICS). Contrary to our results, other investigations have demonstrated that the administration of inhaled corticosteroids (ICS) reduces the frequency of exacerbation events. A meta-analysis examining the utilization of ICS in the emergency department has determined that ICS has the potential to decrease the

likelihood of hospital admissions by 56%, with a confidence interval of 95% ranging from 0.31 to 0.62 [31].

Furthermore, multiple studies have demonstrated that the use of inhaled corticosteroids (ICS) not only decreases the number of asthma-related hospitalizations, but also enhances clinical scores and pulmonary function tests, namely the forced expiratory volume in one second (FEV1). Additionally, ICS usage leads to a decrease in the need for bronchodilators and results in shorter hospital stays [32].

Our study found a statistically significant difference between the groups being evaluated in terms of the usage of systemic steroids and the presence of wheezes. Within the controlled asthma and asthma with exacerbation groups, approximately 28% and 61% respectively utilized steroid medication. Wheezes were present in all individuals experiencing exacerbation of asthma, while only 50% of those with controlled asthma exhibited wheezes. All instances of asthma exacerbation necessitate hospital referral due to the deterioration of asthma symptoms, such as coughing and wheezing. These episodes are managed with the administration of systemic steroids and short-acting bronchodilators.

The study found a significant difference between the groups being studied in terms of sputum clusterin . Children with controlled asthma had higher levels of clusterin compared to non-asthmatic controls [14.82(13.74–16.59) ng/mL vs 11.75(10.82-12.54)ng/mL]. This finding supports previous research that showed elevated levels of clusterin in the serum and sputum of adults and children with asthma [18] [22].

In our study sputum clusterin levels were lower during asthma exacerbation than in controlled asthma[8.13(4.31–9.41) ng/mL **vs** 14.82(13.74–16.59)ng/mL]., clusterin levels might have been lower following corticosteroid treatment because sputum was induced after at least one administration of systemic corticosteroids for most of the children with asthma exacerbation who required systemic corticosteroids.

Our study found a statistically significant correlation between the severity of controlled asthma and serum levels. Clusterin levels were shown to be substantially elevated in cases of severe asthma compared to non-severe asthma, with a p-value of ≤ 0.001. The mean concentration of clusterin in severe asthma was 16.47 ng/mL (range: 15.76–18.12 ng/mL), while in non-severe asthma it was 13.79 ng/mL (range: 12.85-14.03 ng/mL)

There is compelling evidence indicating that both internally and externally generated reactive oxygen and nitrogen species significantly contribute to airway inflammation and are influential factors in the severity of asthma. Moreover, the level of oxidative stress in children with asthma intensifies as the disease becomes more severe [9].

Our study found a statistically significant link between the presence of clusterin in sputum and the presence of eosinophils in sputum. Both of these factors are indicators of airway inflammation .

In contrast to our findings, Sol et al. [22] who discovered in their research that there was no correlation between sputum clusterin levels in asthmatic children and FEV1 or FEF25–75% values, which are indicators of bronchial obstruction. In another study, they discovered that there were no significant associations between serum clusterin and age, as well as pulmonary function indicators such as FEV1%, FVC%, and FEV1/FVC [33].

CONCLUSION

The levels of Clusterin in sputum were modified in children with both controlled asthma and asthma exacerbation due to its antioxidant and anti-inflammatory properties. Clusterin in sputum can serve as an indicator of airway inflammation and the severity of symptoms, making it valuable for evaluating childhood asthma

RECOMMENDATIONS

According to this study, we recommend the following, aiming at proper asthma management in Egyptian populations: Sputum Clusterin level is an important marker in Egyptian asthmatic

children which can be a target of their future treatment plans. Sputum Clusterin level is of good diagnostic value in Egyptian asthmatic children to screen their disease risk. Sputum Clusterin level is of good prognostic value in Egyptian asthmatic children to suspect future disease course. More future studies about Sputum Clusterin level on larger populations be planned to complete our information in our patients as in many cases the studies in one society can't be generalized to others. Clusterin level from broncho-alveolar lavage may be more relevant.

No potential conflict of interest was reported by the authors

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Table (s1) Performance of sputum clusterin in prediction of asthma with exacerbation

Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy	p
≤10.45	0.985	94.4%	91.7%	85%	97.1%	92.6%	<0.001**

AUC area under curve PPV positive predictive value NPV negative predictive value **p≤0.001 is statistically highly significant

Table (s2) Correlation between sputum clusterin and clinical and laboratory parameters

	r	p
Age (year)	-0.187	0.177
FEV1	0.611	<0.001**
FEV1/FVC	0.335	0.013*
Total IgE	-0.148	0.286
WBCS	0.098	0.483
Serum eosinophil	-0.151	0.276
Sputum lekocytic count	-0.058	0.675
Neutrophil (%)	-0.037	0.789
Eosinophil (%)	-0.33	0.015*
Lymphocytes (%)	0.005	0.97

r Spearman rank correlation coefficient **p≤0.001 is statistically highly significant *p<0.05 is statistically significant

Table (s3) Correlation between severity of controlled asthma and sputum Clusterin

	Mild (n=9)	severe (n=9)	Z	p
	Median (IQR)	Median (IQR)		
Sputum clusterin	13.79(12.85-14.03)	16.47(15.76–18.12)	-3.576	<0.001**

Z Mann Whitney test **p≤0.001 is statistically highly significant

Citation

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