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ORIGINAL ARTICLE

Clusterin in atopic and non-atopic childhood asthma

Ahmad Ata Sobeih[a], Ola Galal Behairy[a], Eman Rateb Abd Almonaem[a], Osama Ibrahim Mohammad[b] and Amira Mn Abdelrahman[c]

[a]Department of Pediatrics, Faculty of Medicine, Benha University, Benha, Egypt; [b]Department of Chest, Faculty of Medicine, Benha University, Benha, Egypt; [c]Department of Clinical Pathology, Faculty of Medicine, Benha University, Benha, Egypt

ABSTRACT

Several biomarkers have been studied to diagnose or to detect the phenotype of asthma. Clusterin is a sensitive cellular biosensor of oxidative stress and has been studied as a biomarker for inflammatory diseases. We aimed to study serum clusterin level in atopic versus non-atopic childhood asthma and its relation to disease severity. This case-control study included 160 children; 120 stable asthmatic children and 40 apparently healthy children. Asthmatic children were further subdivided into atopic and non-atopic. All children were subjected to medical history taking, clinical examination, and laboratory investigations including complete blood count, serum IgE, serum clusterin level and spirometry before and after bronchodilator therapy. In comparison to controls, patients had significantly higher eosinophils count which was higher in atopic than non-atopic group, also serum IgE level was higher in the atopic asthmatics (118.1 ± 16.2 U/ml) than in both the non-atopic asthmatics (81.2 ± 6.1 U/ml) and the controls (76.3 ± 11.6 U/ml). There was statistical significant difference in serum levels of Clusterin which were highest in the atopic group (182.5 ± 33.5 ng/l), followed by the non-atopic patients (127.5 ± 32.5 ng/l) and lowest in the controls (46.09 ± 7.01 ng/l). Moreover, the higher the severity of asthma, the higher was the level of serum clusterin. In conclusion serum level of clusterin was higher in atopic than non-atopic asthmatic children and it increases significantly with increased severity of the disease.

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Childhood asthma; atopic asthma; serum clusterin; asthma severity; asthma phenotype

Introduction

Asthma is a heterogeneous disorder characterized by airway hyper-reactivity in response to direct or indirect stimuli, and chronic airway inflammation. It is diagnosed by the presence of respiratory symptoms in the form of wheeze, dyspnea, chest tightness and cough that are variable in intensity and overtime, together with variable expiratory airflow obstruction. Both symptoms and airflow obstruction are initiated by trigger factors such as respiratory infections, exercise, change in weather, or exposure to allergens. The attack may show spontaneous remission or after giving medication [1]. Atopy is strongly associated with asthma. The proportion of atopic asthmatics in children has been estimated to be 38% [2]. Oxidative stress is a cornerstone in the pathogenesis of asthma as it leads to several pathophysiologic changes, such as the increased release of chemoattractants, increased peroxidation of lipid, increased vascular permeability and airway remodeling [3]. Increased oxidative stress may also lead to the development of severe refractory asthma [4]. Clusterin is a glycoprotein found in many types of epithelial cells and categorized as a chaperone protein [5] and a biomarker induced by stress [6]. Clusterin is mostly sensitive to oxidative stress, heat, and radiation [7]. Clusterin causes intra- and extra-cellular interactions with inflammatory molecules, such as complement factors, and transforming growth factor-b (TGF-b), suggesting that it may modulate conditions related to inflammation and immune responses [8]. Circulating clusterin concentration was found to be elevated in patients with severe asthma, and it showed an inverse correlation with lung function; however, clusterin was considered an indicator of oxidative stress rather than a protective factor. It is also correlated with the age of the patients and showed a significant decrease in steroid-naïve patients with the initiation of ICS therapy [8].

So the aim of this study was to evaluate serum clusterin level in atopic vs. non-atopic childhood asthma and its relation to disease severity

Patients and methods

This case-control study took place from May 2017 to May 2018 in the pediatrics and clinical pathology departments of Benha University Hospitals. It included 160 children; 120 steroid naïve stable asthmatic children aged 5–12 years and forty age and sex-matched apparently healthy children with neither past history nor family history of bronchial asthma or any other allergic conditions were taken as controls. The study gained approval of local ethical committee of Benha University. Informed written consent was obtained from the parents or caregivers of enrolled children after explanation

CONTACT Osama Ibrahim Mohammad osama.thorax@yahoo.com Department of Chest, Faculty of Medicine, Benha University, Benha, Egypt

of the study. Subjects were divided into the following groups:

Group I: 80 atopic asthmatic children. Group II: 40 non-atopic asthmatic children. Both group I and group II were diagnosed and verified according to the Global Initiative for Asthma (GINA) Guidelines for Asthma Severity and Control [9] after consideration of Exclusion criteria which include:

- Children receiving antimicrobial therapy.
- X-rays showing other lung findings as collapse, pneumonia, pleural disease, etc.
- Parasitic infestation.

Group III: 40 apparently healthy controls.

The children were subjected to the following

Full history is taken with special attention to intermittent attacks of cough, expectoration, wheezy dyspnea, and chest tightness. Detailed physical examination was performed to detect tachypnea, signs of hyperinflation, prolonged expiratory phase and expiratory rhonchi. Evaluation of lung functions by Spirometry (performed by Erich jaejre 95 GmbH 1992–1997 for measurement of pulmonary function) were performed before and after bronchodilator (administration of four separate puffs at 30-s intervals of the short-acting B2-agonist salbutamol (a total of 400 mcg) using a spacer device) [10] with measuring the following indices: Forced vital capacity (FVC), forced expiratory volume in 1st second (FEV1) and FEV1/FVC and post-bronchodilator change in FEV1 which are displayed automatically by the apparatus.

Laboratory investigations were done for all enrolled subjects including complete blood count analyzed by sysmex Kx-21N with microscopic manual differential count, total serum IgE level measurement by ELISA (DiaMed Eurogen, Turnhout, Belgium) and determination of serum clusterin level measurement by Enzyme-Linked Immunosorbent Assay (ELISA) kit designed for the quantitative measurement of clusterin level in supernatants, buffered solutions, serum, and plasma samples (Monobind Inc., LaForest, CA, USA).

Statistical analysis

Data management and statistical analysis were performed using the Statistical Package for Social Sciences (SPSS) vs. 23 (IBM, Endicott, Broome_County, NY, USA). Numerical data were summarized using means and standard deviations; differences between the three groups were done using ANOVA or Kruskal–Wallis test. Categorical data were summarized as numbers and percentages, differences were analyzed with χ^2 (Chi-square) test or Fisher exact when appropriate. All pair-wise comparisons were adjusted using Bonferroni correction. Correlations were done using Spearman correlation; "r" is the correlation coefficient.

Results

Our study included Group I: 80 atopic children, 48 (60%) males and 32 (40%) females. Their mean age was 7.2 ± 1.9 years. Group II: included 40 non-atopic children, 22 (55%) males and 18 (45%) females, their mean age was 6.92 ± 2.7 years. Group III (control): included 40 apparently healthy children, 20 (50%) males and 20 (50%) females. Their mean age was 6.1 ± 2.5 years. Concerning grades of asthma severity; there were 22 cases (27.5%) in group I and 22 (55%) in group II with mild persistent asthma, 46 cases (57.5%) in group I and 14 (35%) in group II with moderate persistent asthma and 12 cases (15%) in group I and 4 (10%) in group II with severe persistent asthma.

In comparison to controls, patients had significantly higher eosinophils count which was higher in a topic than non-atopic group, also serum IgE level was higher in the atopic asthmatics (118.1 ± 16.2 IU/ml) than in both the non-atopic asthmatics (81.2 ± 6.1 IU/ml) and the controls (76.3 ± 11.6 IU/ml). There was a statistically significant difference in the serum levels of clusterin which was highest in the atopic group (182.5 ± 33.5 ng/l), followed by the non-atopic patients (127.5 ± 32.5 ng/l) and lowest in the controls (46.09 ± 7.01 ng/l) (Figure 1). There were statistically significant differences between the studied groups regarding pulmonary function parameters as it was significantly higher in the control group (Table 1).

There were statistically significant differences between different degrees of asthma severity regarding serum clusterin level as it increases significantly with increased asthma severity ($p < .001$); while there were no statistically significant differences between serum IgE levels in the different degrees of asthma severity (Table 2).

There was a statistically significant positive correlation between serum clusterin and eosinophilic percentage ($r = 0.532$; 95% confidence interval for "r"=0.368–0.634, p-value < .001), serum IgE ($r = 0.859$; p-value < .001). However, serum clusterin showed no significant correlations with age and pulmonary function parameters (FEV1%, FVC% and FEV1/FVC).

Discussion

In the current study, we found a significantly higher level of serum IgE in the atopic group when compared with either the non-atopic or the control groups. Atopic status can be identified by the level of specific IgE [1]. Stein and Martinez stated that in non-atopic asthmatic children attacks of wheezing are not associated with elevation of total serum IgE [2].

The eosinophilic count was much higher in our atopic group followed by the non-atopic one followed by the controls. Eosinophils may play a role in airway hyper-responsiveness in asthma by the effects of granular proteins derived from eosinophil on the bronchial tree. It has been assumed that a defect in eosinophil programmed cell death would play a role in the occurrence and persistence of allergic airway inflammation in asthma [11]. Diagnosis of

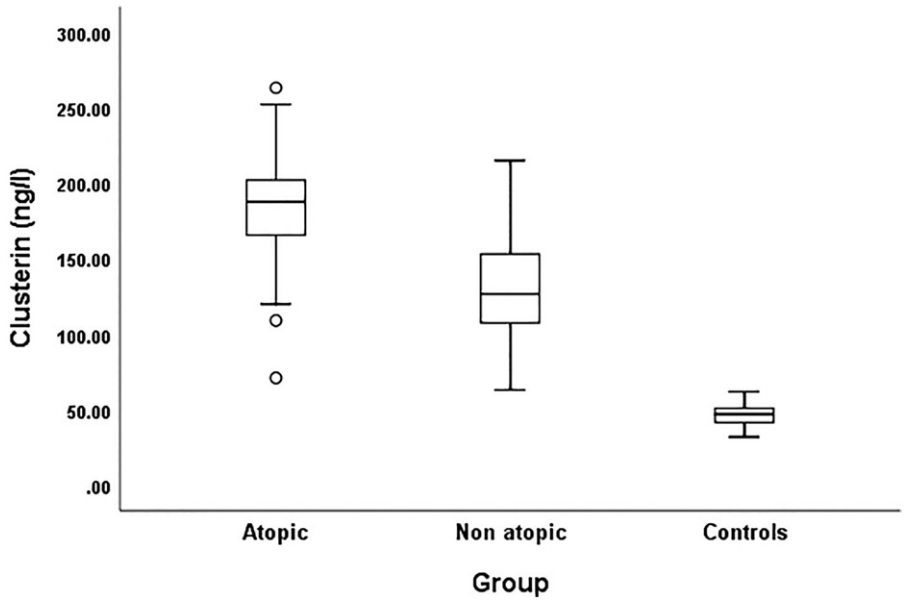

Figure 1. Box and Whisker diagram for clusterin between study groups.

Table 1. Serum IgE & clusterin levels in the studied group.

Variables	Atopic group, mean ± SD	Non-atopic group, mean ± SD	Control group, mean ± SD	*F* test	*p*-value
Serum clusterin (ng/l)	182.5 ± 33.5	127.5 ± 32.5	46.09 ± 7.01	150.2	<.001(HS)
Serum IgE (IU/ml)	118.1 ± 16.2	81.2 ± 6.1	76.3 ± 11.6	67.1	<.001(HS)
Eosinophils cells $\times 10^9$/L	4.5 ± 1.69	1.5 ± 1.80	1.4 ± 0.50	=137.5	<.001(HS)
FEV1%	70.2 ± 5.12	72.2 ± 4.14	95.87 ± 2.98	76.2	<.001(HS)
FVC%	72.4 ± 4.45	75.1 ± 6.06	98.23 ± 7.91	79.3	<.001(HS)
FEV1/FVC	69.4 ± 2.79	65.2 ± 3.45	89.2 ± 3.7	74.8	<.001(HS)

HS: high significance; FVC: forced vital capacity; FEV1: forced expiratory volume in 1st second

Table 2. Serum clusterin & IgE in different degrees of asthma severity.

Variables	Mild persistent asthma, mean ± SD	Moderate persistent asthma, mean ± SD	Severe persistent asthma, mean ± SD	*F* test	*p*-value
Serum clusterin (ng/l)	136.7 ± 31.5	199.4 ± 12.4	264 ± 6.3	145.5	<.001
Serum IgE (IU/ml)	86.4 ± 17.4	112.4 ± 19.1	156.6 ± 26.9	=124.2	.343

eosinophilic airway inflammation can be supported by the presence of blood eosinophilia [1].

In the present study, the results of serum clusterin concentration showed that there was a statistically significant difference between the controls and the asthmatics, where the highest level of clusterin was found in the atopic asthmatics followed by the non-atopic ones and then the controls. The results of Sol et al. and Dombai et al. [12,13] declared that the level of serum clusterin is higher in the asthmatics than in the controls and supports a previous study that demonstrated high clusterin levels in serum and sputum from asthmatic adults. The elevated clusterin in childhood asthma might also be attributed to oxidative stress, which contributes to asthma development [8].

Our study shows that the higher the severity of asthma, the higher the level of serum clusterin with highly statistically significant differences between the different degrees of asthma severity ($p < .001$). These results are consistent with Kwon et al. [8] who stated that clusterin may be a biomarker of asthma severity and the degree of oxidative stress in asthmatic patients. In addition, they found that serum clusterin levels were inversely correlated with FEV1 ($p = .024$) in all the patients with asthma. Their data also indicated that serum clusterin level after treatment with inhaled corticosteroids (82.1 mcg/ml) was significantly lower than that before the use of ICS (76.3 mcg/ml).

Endogenous and exogenous reactive oxygen and nitrogen species are strongly associated with airway inflammation and are contributing factors of asthma severity [14]. The presence of strong oxidative stress in asthmatic children also increases with an increased degree of disease severity [4]. Clusterin is a sensitive cellular biosensor of oxidative stress that protects cells from the harmful effects of free radicals and their byproducts, and it inhibited the toxic effects of oxidants in numerous studies [15]. Based on this, the increase in clusterin levels with asthma severity is likely related to the oxidative stress in asthmatic patients.

In the current study, we found positive correlations between serum clusterin level and both the eosinophilic count and serum IgE. However, serum clusterin showed no significant correlations with age and pulmonary function parameters (FEV1%, FVC% and FEV1/FVC). Suk Sol et al. found that sputum clusterin was higher in eosinophilic airway inflammation than in non-eosinophilic airway

inflammation; furthermore, sputum clusterin showed a weak positive correlation with eosinophil dominant airway inflammation. This indicates that increased clusterin with eosinophilic airway inflammation is consistent with childhood asthma. In their study, sputum clusterin levels in asthmatic children were not related with FEV1 or FEF25 – 75% values, which represent airflow limitation; however, they inversely correlated with PC20, which signifies airway hyper responsiveness [12].

Conclusion

Serum level of clusterin was higher in atopic than non-atopic asthmatic children and it increases significantly with increased severity of the disease.

Disclosure statement

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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