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Assessment of Ceruloplasmin, Hemopexin, and Haptoglobin in Asthmatic Children

Amany M. Abd Al-Aziz¹, Hala Shaaban², Ahmed A. Talaat^{1*}, Mona A. M. Awad³, Radwa Ali¹, Walaa A. Shahin²

¹Department of Pediatric, National Research Centre, Cairo, Egypt; ²Department Pediatric, Faculty of Medicine, Cairo University, Cairo, Egypt; ³Department Clinical and Chemical Pathology, National Research Centre, Cairo, Egypt

Abstract

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***Correspondence:** Ahmed A. Talaat, Department of Pediatric, National Research Centre, Cairo, Egypt. Phone: 00201001608014. E-mail: atalaat62@gmail.com
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BACKGROUND: Ceruloplasmin (Cp), haptoglobin, and hemopexin play a role in iron homeostasis and may function to modulate the systemic inflammatory response and be involved in tissue repair. We hypothesized that these proteins could be biological markers for bronchial asthma that reflect the involvement of iron oxidative stress in asthma pathogenesis.

AIM: Evaluation of serum levels of proteins involved in iron homeostasis (Cp, hemopexin, and haptoglobin) in asthmatic children and their correlation to pulmonary functions.

MATERIALS AND METHODS: Sixty moderate to severe persistent asthmatic children aged 6–13 years were included (30 during attacks and 30 in-between attacks). Thirty healthy matched controls were also recruited. All children were subjected to history taking, clinical evaluation and assessment of complete blood picture, serum levels of Cp, haptoglobin, hemopexin, and total IgE. Pulmonary function tests were assessed for all patients.

RESULTS: Serum Cp and haptoglobin were significantly elevated in asthmatic children between attacks (448.04 ± 386.79), (993.33 ± 554.56) compared to controls (168.42 ± 13.46), (473.33 ± 350.3), ($p = 0.0002$, $p < 0.0001$) and to asthmatics during exacerbations (288.8 ± 219.6), (620 ± 467.86), ($p = 0.014$, $p = 0.006$). Serum hemopexin was significantly higher in asthmatics between attacks (509.33 ± 341.51) compared to controls (296.67 ± 158.38) ($p < 0.003$) but no significant difference compared to acute exacerbations (477.33 ± 396.6). No significant correlations were found between any of the assessed protein levels and pulmonary functions. Hemoglobin concentration was significantly higher among stable asthmatics compared to acute exacerbation and control groups.

CONCLUSION: Cp, haptoglobin, and hemopexin can be used as a panel of non-invasive biomarkers that reflect the involvement of iron oxidative stress in asthma pathogenesis.

Introduction

Bronchial asthma has emerged as the most common non-communicable respiratory disease affecting children worldwide [1], and its prevalence is increasing. The causes and pathogenesis of bronchial asthma are not completely understood [1], [2], and it is becoming increasingly apparent that the disease is heterogeneous with respect to immune-pathology, clinical phenotypes, response to therapies, and natural history [3]. Precision in diagnosis and treatment has become imperative for the achievement of better outcomes [4]. In practice, a panel of biomarkers is needed to indicate the various underlying disease pathologies and enable the definitive categorization of asthmatics into distinct sub-phenotypes [5].

A potential for iron-catalyzed oxidative stress in asthma was reported [6], and proteomic discovery program has identified a panel of proteins indicating the involvement of iron metabolism pathway in asthma [7]. Ceruloplasmin (Cp), haptoglobin, and hemopexin are

predominantly liver-synthesized acute phase proteins that play a role in iron homeostasis and have important anti-inflammatory activity through inhibition of oxidative stress and iron sequestration resulting in antimicrobial activity [7], [8].

Cp regulates body iron homeostasis by its capacity to oxidize the highly toxic ferrous form of iron to the relatively nontoxic ferric form. Cp is required for efficient iron release from cells and tissues [9]. The inhibition of heme releases from globin by haptoglobin and sequestration of heme by hemopexin, suppress hemoglobin-mediated oxidative stress, attenuates endothelial cytotoxicity, and protects cells from heme toxicity [10].

These proteins may function to modulate the systemic inflammatory response to inflammation and be involved in tissue repair through fibrosis and angiogenesis [7]. We hypothesized that these proteins could be biological markers for bronchial asthma that reflect the involvement of iron in asthma pathogenesis and protect against iron oxidative stress.

We aimed to evaluate the serum levels of proteins involved in iron homeostasis (Cp, hemopexin, and haptoglobin) in asthmatic children and their correlation to pulmonary functions.

Materials and Methods

The study was case–control one, included 60 chronic asthmatic children aged 6–13 years 30 recruited during attacks (Group I) and 30 recruited in-between attacks (Group II), they were recruited from Pulmonology and Allergy Clinic, Children's Hospital, Cairo University. Inclusion criteria: Patients suffering from asthma solely, based on careful history and physical examination as well as a documented reversible and variable airflow obstruction as described in GINA were included in the study [11].

Exclusion criteria

Patients with mild persistent or intermittent asthma, patients receiving inhaled corticosteroids or leukotriene antagonists within 1 week or receiving oral corticosteroids within 3 weeks before inclusion in the study, patients suffering from other chronic illnesses (diabetes mellitus, kidney disease, liver disease, or thyroid dysfunction), conditions that can alter acute phase reactants including patients with acute (within 1 week) and chronic inflammatory disorders, patients with neuromuscular disorders, patients with hemolytic anemia, Wilson's disease, lymphoma, and rheumatoid arthritis. Thirty non-atopic, non-asthmatic age- and sex-matched healthy control children (Group III) were also included. They were recruited from Ophthalmology Clinic, Children's Hospital, Cairo University. The study has been approved by the Ethical Committee of the National Research Centre. All patients' guardians gave informed written consent.

All candidates were subjected to detailed history taking, clinical evaluation, and assessments of pulmonary function tests (for patients). Venous blood samples were collected from all included children for the assessment of complete blood count, total serum IgE level (using ELIZA DRG International Inc Kit (USA), and assessment of serum Cp, hemopexin, and haptoglobin (using ELIZA assay pro Kits (Missouri, USA).

Statistical analysis

Data were analyzed using the GraphPad prism version 6. t-test was used to compare between two groups, and ANOVA test was used for comparison between more than two groups. For quantitative

variables, mean, standard deviation was presented. Correlation to estimate the association between quantitative variables was presented in the form of correlation coefficient (r) and its significance. $p < 0.05$ was considered statistically significant.

Results

The study included 19 males (53.3%) and 11 females (36.7%) in Group I, 16 male (63.3%) and 14 females (46.7%) in Group II, no significant difference was detected ($p = 0.601$) between both. Positive family history was present in 24 (80%) of Group I and 15 (50%) of Group II. Comparison between asthmatics (Groups I and II) and controls regarding demographic, clinical, and lab data are presented in Table 1.

The mean serum level of Cp exhibited significantly higher values in Group II compared to Group I ($p = 0.014$) and in both Groups I and II, compared to controls ($p = 0.004$ and $p = 0.0002$ respectively), Table 1 and Figure 1.

The mean serum level of haptoglobin exhibited higher values in Group II compared to Group I ($p = 0.006$) and control subjects ($p < 0.0001$). The difference between Group I and control was insignificant ($p = 0.1$) (Table 1 and Figure 2).

The mean serum level of hemopexin exhibited higher values in Group I and Group II compared to control subjects ($p = 0.02$, 0.003 , respectively) but the difference between both Groups I and II was insignificant ($p = 0.7$), (Table 1 and Figure 2).

No significant correlations were found between any of the previous protein levels assessed and pulmonary functions or any other variable in the study, as presented in Table 2.

Discussion

Identifying biomarkers involved in asthma pathogenesis could have a possible role in bridging the diagnostic gap [4] and the creation of personalized treatment regimens [5]. The current study demonstrated differential expressions of Cp, haptoglobin, and hemopexin among our clinical groups.

Cp is a sensitive acute phase reactant, which increases during acute and chronic inflammatory processes [12]. There is experimental evidence that some cell types in the lungs and airways may have the potential to produce Cp [13]. It has significant antioxidant capacity and can reduce lipid peroxidation

Table 1: Demographic, clinical, and lab data of the studied groups

Variable	Group I) asthmatics during acute attacks (n=30) Mean±SD	Group II asthmatics between the attacks (n=30) Mean±SD	Group III controls (n=30) Mean±SD	p-value
Age (years)	9.5±2.366	8.4±2.14	8.96±2.01	0.08 between Groups I and II 0.97 between Group III and all asthmatics age (8.977±2.34)
Age of onset of asthma (months)	26.9±20.2	22.6±18.3		0.4
Height (cm)	134.3±15.64	128.5±14.81	132.1±12.2	0.14
Weight (kg)	32.77±12.36	29.07±10.6	31.65±10.5	0.21
Body mass index	17.45±3.06	16.8±2.4	17.8±2.8	0.4
Hemoglobin (g/dl)	12.47±1.01	13.4±1.3	12.2±1	Group I versus II=0.002* Group I versus control=0.4 Group II versus control=0.0003* Group I versus II=0.7
Platelets X 10 ³ /ul	297.7±91.7	289.2±81.5	259.8 ± 70.05	Group I versus control=0.07 Group II versus control=0.1 Group I versus II=0.03*
Leukocytic count X 10 ³ /uL	11.5±4.14	9.5±3.2	6.2±2.5	Group I versus control <0.0001* Group II versus control <0.0001* Group I versus II=0.004*
Absolute eosinophil count/cu mm	833.67±351.09	569.6±336.92	135±34.63	Group I versus control <0.0001* Group II versus control <0.0001* Group I versus II=0.007*
IgE (IU/ml)	235.52±159.2	125.64±149.9	55.11±20.75	Group I versus control <0.0001* Group II versus control=0.01* Group I versus II=0.014*
Ceruloplasmin (mg/dl)	288.8±219.6	448.04±386.79	168.42±13.46	Group I versus control =0.004* Group II versus control=0.0002* Group I versus II=0.006*
Haptoglobin (µg/ml)	620±467.86	993.33±554.56	473.33±350.3	Group I versus control=0.1 Group II versus control <0.0001* Group I versus II =0.7
Hemopexin (µg/ml)	477.33±396.6	509.33±341.51	296.67±158.38	Group I versus control =0.02* Group II versus control =0.003*

*p<0.05 is significant.

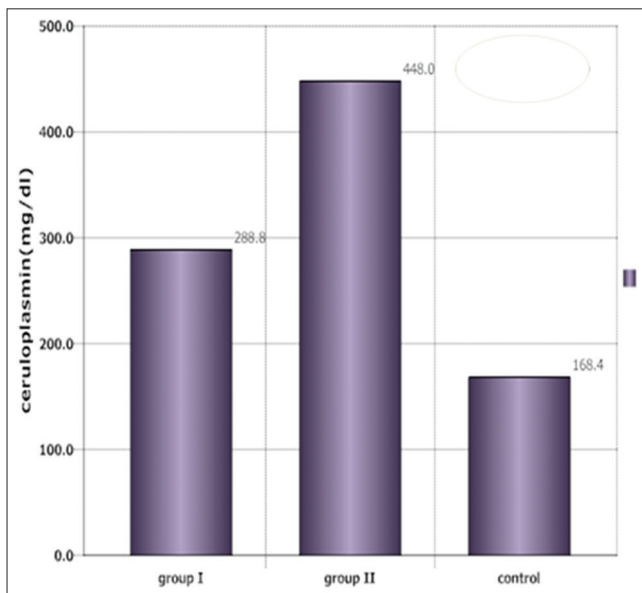


Figure 1: Comparison between mean serum levels of ceruloplasmin in Group I, Group II, and control children

induced by metal ions and peroxy radicals, which in turn decreases cellular damage induced by toxic peroxidation products [14].

In our study, there was a significant higher Cp serum level in stable asthma and acute asthma exacerbation groups compared to controls. This agreed with Verrills *et al.* [7], Ermis *et al.* [15], and Vural and Uzun [16] who found significant higher Cp serum level in stable asthmatics compared to controls. Cp was significantly lower in acute asthma exacerbation when compared to stable asthma. This may be due to consumption during acute attacks for protection of the

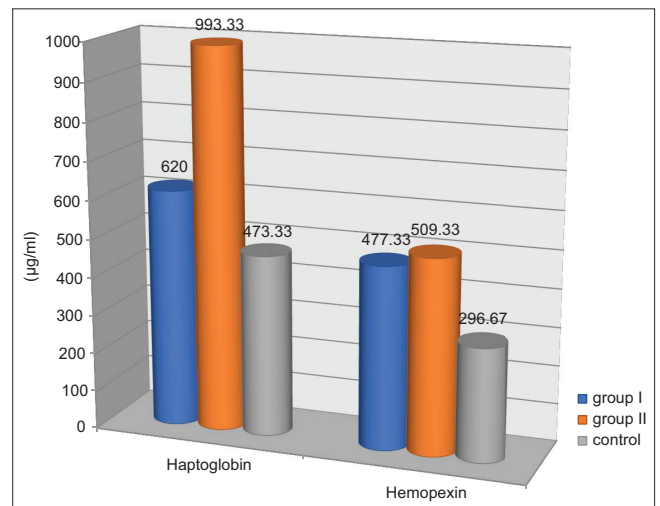


Figure 2: Comparison between Group I, Group II, and control subjects regarding mean serum levels of haptoglobin and hemopexin

lungs, as reported by Farkhutdinov and Farkhutdinov [17] who indicated that Cp use in the combination therapy of asthma exacerbation resulted in a reduction in reactive oxygen species generation and contributed to positive changes in the clinical symptoms of asthma. Another explanation is a possibility of leakage of this protein from the blood to tissue during acute exacerbations; this assumption was supported by Van Rensen *et al.* [18] who reported increased concentrations of Cp in the sputum of asthmatics 30 min following inhalation challenge with substance P as compared to before the challenge; moreover, the sputum-to-serum ratios for Cp increased significantly after the challenge.

Haptoglobin is increased in alveolar macrophages and eosinophils in diseased or inflamed

Table 2: Correlations between ceruloplasmin, haptoglobin, hemopexin, and different variables in asthmatic children

Variable	Ceruloplasmin in all asthmatics n=60		Haptoglobin in all asthmatics n=60		Hemopexin in all asthmatics n=60	
	r	p	r	p	r	p
Age (years)	-0.12	0.35	-0.1	0.4	-0.06	0.5
Age of onset of asthma (months)	-0.07	0.5	-0.11	0.3	0.21	0.1
IgE (IU/ml)	-0.01	0.9	0.06	0.6	-0.02	0.8
Absolute eosinophilia count (cells/cu mm)	-0.0004	0.99	-0.07	0.5	0.02	0.8
Forced expiratory volume 1 % pred.	0.13	0.32	-0.2	0.1	-0.02	0.82
Forced vital capacity % pred.	0.15	0.25	-0.24	0.06	0.019	0.88
Forced expiratory flow 25-75% pred.	-0.02	0.82	-0.08	0.5	-0.08	0.52
Peak expiratory flow % pred.	-0.014	0.91	-0.03	0.8	-0.008	0.9
Haptoglobin (µg/ml)	0.1	0.17				
Hemopexin (µg/ml)	-0.1	0.43				
Correlation between haptoglobin and hemopexin			0.009	0.9		

tissues providing antioxidant and antimicrobial activity [19]. In our study, stable asthmatics exhibited significantly higher serum levels of haptoglobin compared to control subjects. This was consistent with the results demonstrated by Verrills *et al.* [7] and Kauffmann *et al.* [20]. The serum level of haptoglobin exhibited significant higher values in stable asthmatics compared to acute exacerbation. This agreed with Nishioka *et al.* [21]. Haptoglobin may be infused into the airways during the inflammatory process, which was supported by Larsen *et al.* [22]. Lamoureux *et al.* [23] have found that serum haptoglobin concentrations were significantly elevated in equine models of asthma during disease remission and after antigenic exposure compared to the control group. Variable serum levels of haptoglobin have been reported in asthma, either elevated [24], [25] or reduced [26]. Elevated haptoglobin in stable asthmatics (Group II) could be due to its involvement in tissue repair function [22] or to the kinetics of hepatic cellular response to cytokines [24]. The salivary concentrations of haptoglobin were found to be significantly higher in allergic asthmatic children [27].

A minor part of erythrocytes undergoes intravascular destruction, releasing hemoglobin which is bound by haptoglobin and the complexes is subsequently delivered to reticuloendothelial system, where they are internalized through receptor-mediated endocytosis. Haptoglobin, by binding hemoglobin and removing it from the circulation, prevents the iron-stimulated formation of oxygen radicals and has an important role as an antioxidant [28]. Consistent with its role in modulating immune responses, haptoglobin at high levels was found to be related to AHR in asthma [25]. As part of its tissue repair function, haptoglobin can induce differentiation of fibroblast progenitor cells into lung fibroblasts and angiogenesis, potentially implicating haptoglobin in remodeling and fibrosis in asthma [22].

Hemopexin: In the current study, stable asthmatics exhibited higher mean serum levels of hemopexin compared to controls. This was consistent with the result of Verrills *et al.* [7]. Furthermore, we

found higher serum levels of hemopexin during acute exacerbations compared to controls, which agreed with Haenen *et al.* [29] in murine models induced asthma. The serum level of hemopexin during acute exacerbations showed tendency to be lower than stable asthmatics, yet the change was statistically insignificant. This reduction may be justified by the expression of hemopexin in the airways, the same as haptoglobin do. Monferran *et al.* [30] have shown that the hemopexin domain of matrix metalloproteinase-9 (MMP-9) is important for the interactions of the metalloproteinase with the Ku heterodimer (Ku70/Ku80), a protein that plays a central role in DNA breaks repair. Interactions of Ku and MMP-9 have been reported to be involved in remodeling of the extracellular matrix, which is a major cause of airway remodeling in asthma and is closely related to airway wall fibrosis and airflow limitation [31]. Studies found that the plasma level of total MMP-9 was significantly increased in patients with asthma in acute exacerbation and decreased in remission but remained elevated compared to healthy controls [32], [33]. These data suggest that hemopexin may be consumed during asthma exacerbation being an important factor for the activity of MMP-9.

The reduction in serum haptoglobin level during exacerbation compared to stable asthma was more noticeable than the reduction in hemopexin; this may be explained by the fact that only once haptoglobin is depleted, do levels of hemopexin begin to fall as reported by Muller-Eberhard *et al.* [34]. When the buffering capacity of haptoglobin is exceeded, hemoglobin liberates heme, which binds to albumin and is subsequently transferred to hemopexin [35]. Hemopexin binds heme with high affinity and delivers it to the liver to provide protection against free heme-mediated oxidative stress and to limit access by pathogens to heme. This contributes to iron homeostasis by recycling heme iron [36]. Free heme is highly toxic as it is a source of redox-active iron. In the cytoplasm, iron can participate in the Fenton reaction to produce the highly toxic reactive oxygen species that damage lipid membranes, proteins, and nucleic acids [37]. Significantly increased levels of hemopexin and haptoglobin, in broncho-alveolar lavage fluid of asthmatic patients compared to control subjects was reported [38].

No correlations were detected in the present study between the levels of Cp, haptoglobin, and hemopexin serum markers in all asthmatic patients and age. This agreed with Verrills *et al.* [7]. Serum Cp, haptoglobin, and hemopexin were not correlated to each other or to other different variables in the study (sex, age of onset of asthma, total serum IgE, and total eosinophilic count). Similarly, no correlation was found between Cp, haptoglobin, hemopexin, and lung functions. Vural and Uzun [16] demonstrated similar results concerning Cp.

Higher serum total leukocytic count was demonstrated during acute exacerbations and stable asthmatics compared to control subjects. These

observations were agreed with Galez *et al.* [39]. Razi *et al.* [40] had similar data regarding acute exacerbation. Significantly elevated total leukocytic count during asthma exacerbation compared to stable asthma was found; this agreed by Belda *et al.* [41]. This confirmed an association between systemic inflammation and airway inflammation, as previously shown in different studies [42], [43]. Leukocytosis may also happen due to long-term use of β -agonist or steroid use [44].

Hemoglobin concentration was significantly higher among stable asthmatics compared to acute exacerbation group but no significant difference between acute exacerbation and control groups. These results are consistent with the findings of a study done by Weiss and Desforges [45]. Hemoglobin was significantly higher among stable asthmatics group compared to control which agreed with Guo *et al.* [46], Hailemaryam *et al.* [47], and Ejaz *et al.* [48] and might be due to increased erythropoietin production induced under hypoxic conditions [49]. The reduction of Hb concentration during exacerbation may be due to the release of hemoglobin and its derivative heme into tissue compartments where there are infection and inflammation [10].

Conclusion

Cp, haptoglobin, and hemopexin can be used as a panel of non-invasive biomarkers that reflect involvement of iron oxidative stress in asthma pathogenesis.

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