Biomedical & Pharmacology Journal, June 2022. Vol. **15**(2), p. 951-960

Oxidative Stress: Assessment of Thiobarbituric Acid Reactive Substances Value in Overweight Asthmatic Children

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https://dx.doi.org/10.13005/bpj/2430

(Received: 17 March 2022; accepted: 13 June 2022)

Nowadays bronchial asthma and increased body weight represent major problems in children. Asthmatic attacks in obese patients are not well controlled using the conventional treatment regimens. Asthma has been associated with increased systemic and exhaled levels of hydrogen peroxide and thiobarbituric acid-reactive products in expired breath condensate of asthmatic patients. Thiobarbituric acid reactive substances formed from peroxidation of lipids. The aim of the Study is to show the action of Thiobarbituric acid reactive substances activity in asthma among overweight children suffering from asthma and to detect the connection between this biomarker and the etiology, degree of severity among children with bronchial hypereactivity. The study is cross-sectional study, was conducted on Egyptian children on regular follow up at the outpatients pediatric allergy clinic in Bab El-shariea university Hospital, Al-Azhar University. The study group included 96 child divided into 4 groups. Group A which included overweight children with (mild persistent asthma). Group B which included non-overweight children with (mild persistent asthma).Group C which included overweight non-asthmatics children and Group D The control group (non-overweight non-asthmatics). The results showed significant increase in the Thiobarbituric acid reactive substances level in Overweight asthmatic patients in relation to non-overweight patients with asthma. We found that they can distinguish asthma controlled patients from non-asthma controlled patients. This study showed high level of oxidative stress with high asthma severity as measured by Thiobarbituric acid reactive substances. These substances were good markers of relation between bronchial hyper activity and oxidative stress which became high with asthma severity.

Keywords: Athma; Obesity; Severity.

Nowadays bronchial asthma and increased body weight represent major problems in children; their number became very high in the last years and had reached a stationary phase[1, 2, 3]. Bronchial asthma is chest problem caused by inflammation with symptoms different in date and power. There is a complex connection between endogenous and genetic factors and outer cause of physical,

chemical, pharmacological, and immunological facts causing excessive secretion production, spasm of the bronchial tree, mucosal inflammation and fibrosis[1].

Obesity is an important predisposing factor for asthma; however, mechanisms of action are not clear. Moreover, asthmatic attacks in obese patients are not well stabilized when the conventional treatment is used[4]. Many factors interfere with asthma treatment like some associated metabolic factors[5], which include high lipids level and increased body weight[6].

Oxidative stress is imbalance between oxidative and anti oxidative processes causing development of large amounts of oxidation products, which can't be measured easily. In the airways, assessment the count of lipid peroxides is a good marker for the degree of oxidative stress, Lipid peroxides are stable non-enzymatic by-products of oxidation. Asthmatic patients usually have high systemic and exhaled levels of hydrogen peroxide and thiobarbituric acid-reactive products in expired breath condensate of asthmatic patients[7]. These biomarkers are accompanied with decline in the lung function and deterioration in the degree of severity of bronchial asthma.[8-11]

The link between degree of difficulty of asthma and oxidative antioxidant degree still not clear. Previous researches showed high count of oxidatives in relation to deterioration of bronchial asthma; however, no proof of antioxidants deficiency in severe asthma[12]

Thiobarbituric acid reactive substances (TBARS) are developed from peroxidation of lipids (degradation products of fats)[13]

TBARS test detects malondialdehyde (MDA) found in the body, also malondialdehyde produced by lipid hydroperoxides through process of hydrolysis. MDA is a low-molecular-weight end product developed through the degeneration of many products of the process of lipid peroxidation[14]

Aim of the Study

To evaluate the role of TBARS among overweight patients suffering from asthma and to determine the connection between this biomarker and the etiology and degree of severity among patients suffering from asthma.

Patient and Method

The study is cross-sectional study, was conducted on Egyptian children on regular follow up at the outpatients pediatric allergy clinic in Bab El-shariea university Hospital, Al-Azhar University from July 2021to August 2022.

The study group included 96 child (girls and boys) aged between (6-14) years and divided into 4 groups : Group A which included 24 overweight (BMI 25-29) children with (mild persistent asthma).

Group B which included 24 non-overweight children with (mild persistent asthma). Group C which included 24 overweight non-asthmatics children and Group D The control group (non-overweight non-asthmatics) 24 apparently healthy matched age and sex with no history of allergic problems .

The patients were classified into overweight and non-overweight groups according to the body mass index (BMI).

The diagnosis of asthma according to the guidelines (the Global Initiative for Asthma) depended on presence of previous long term or repeated pulmonary problems like cough, wheezes, dyspnea and tight chest which show good relieve with using short-acting bronchodilator.

The Degree of asthma severity detected by dynamic spirometry pre & post- bronchodilators which were done by a handled computerized spirometer (Spirostik equipment and blue cherry software from Gerathem Respiratory, 2016).

The following data were obtained; forced vital capacity FVC (liter), forced expiratory volume in the first, second FEV1 (liter), FEV1/FVC ratio or FEV1%. For every parameter obtained, actual and predicted values for age, sex, height, weight and percentage (%) of the predicted will be calculated. The highest values of three forced expiratory maneuvers were used. These parameters measured according to guidelines of the European Respiratory Society and the American Thoracic Society.

Data about the patients were taken from parents including: age, gender, consanguinity, family history, duration of illness and drugs used.

All the asthmatic children who were enrolled in this study didn't receive any anti-inflammatory treatment such as corticosteroids or leukotriene antagonists in the last six weeks , and didn't develop upper or lower respiratory tract infection or asthma exacerbation.

Children with long term cardiac, hepatic or

renal problems, autoimmune disorders, infections and Diabetes mellitus together with those who have been receiving vitamins, antioxidant drugs, hormonal drugs and diuretics were excluded from this study.

Laboratory Investigation

Blood samples were collected from the study group and put in chilled tubes containing EDTA as anticoagulant. Then the plasma separated by centrifugation at 3000 xg in 20 minutes and kept in-20º until analysis. Blood was then stored on ice between the time of sampling and centrifugation. The following tests were performed: full blood picture (CBC),Erythrocyte sedimentation rate (ESR),C -reactive protein (CRP),lipid profile (cholesterol and triglycerides),Glycated Hb (Hb A1c) and Thiobarbituric acid reactive substances (TBARS)

Statistical analysis

Files were put on the PC and analysis performed by software package version 20.0. (Armonk, NY: IBM Corp).The Kolmogorov-Smirnov was performed to see the normal distribution of variables. Differences of categorical variables between study groups were assessed by Chi-square test (Monte Carlo correction). Student t-test was used in normally distributed quantitative data. Mann Whitney test was used for not normally distributed quantitative data while function of ANOVA test was to compare between the four studied groups and followed by Post Hoc test (Tukey) for pairwise comparison. And we used Kruskal Wallis test show abnormally distributed quantitative data and followed by Post Hoc test (Dunn's for multiple comparisons test) for pairwise comparison. Significance of the obtained results was measured at the 5% level.

RESULTS

Research was conducted on 96 patient who were divided into 4 groups The demographic data, anthropometric measurement and laboratory investigation are present in table 1 .there was significant difference regarding BMI which was higher in group 1 and 2 compared to other groups .there was also significant difference in the level of HDL between group 1 and the other groups .there was significant increase in the TBARS level in group 1 when compared with the other groups.

In table 2 the study groups were classified into 2 groups' asthmatics and non-asthmatics and there was no significant correlation between 2 groups regarding laboratory investigations and TBARS levels.

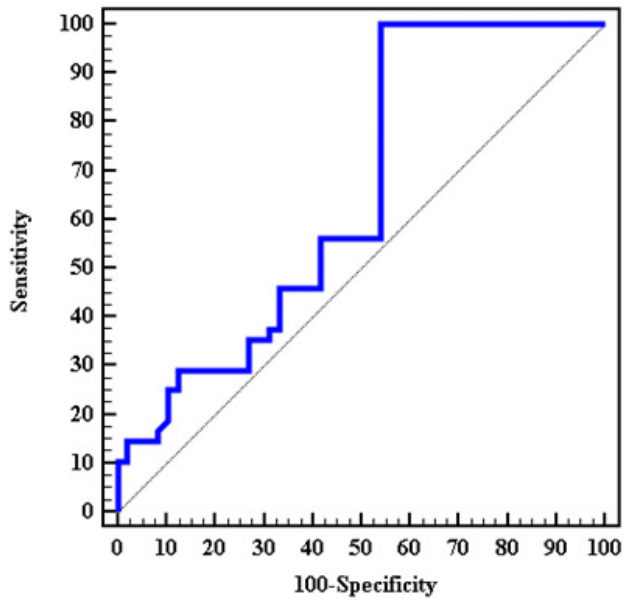

Fig. 1. ROC curve for TBARS (nmol/ml) to diagnose asthmatics patients (n = 48) from non-asthmatics patients (n = 48)

There was significant increase in the TBARS level in uncontrolled Asthmatic patients when compared to the controlled one as seen in table 3

In table 4 the asthmatic children (n=48) were subdivided into 4 groups depending on weight and status whether controlled or not .there was significant increase in the TBARS levels in the overweight asthmatic uncontrolled group and the nonoverweight asthmatic uncontrolled group also when compared with the other 2 groups.

In Figure 1 and table 5 we illustrated that TBARS can diagnose asthmatic patients with cut off value >0.3 and with both sensitivity and specificity 56.25% and 58.33 % respectively

Univariate and multivariate logistic regression analysis were used to detect parameters affecting level of TBARS as obesity, BMI and HDL as shown in table 6.

In Figure 2 and table 7 we found that TBARS can distinguish asthma controlled patients from non asthma controlled patients with cut

Table 1. Demographic data, anthropometric measurement and investigations of the study groups

	Group 1 (n = 24)	Group 2 (n = 24)	Group 3 (n = 24)	Group 4 (n = 24)	Level of Sig. (p)
Sex					
Male	10 (41.7%)	8 (33.3%)	14 (58.3%)	15 (62.5%)	χ^2=5.461
Female	14 (58.3%)	16 (66.7%)	10 (41.7%)	9 (35.7%)	(0.141)
Age (years)					
Mean ± SD.	7.7^a ± 2.2	7.9^a ± 2	6.9^a ± 1.7	6.9^a ± 1.9	F=1.772
Median (Min. – Max.)	7.4 (5 – 12)	7.3 (5.2 – 11.8)	6.9 (4.3 – 10.2)	7.1 (4.2 – 10.2)	(0.158)
BMI (kg/m^2)					
Mean ± SD.	27.6^a ± 1.2	27.2^a ± 1.1	18.9^b ± 2.1	18.4^b ± 2.5	F=184.144*
Median (Min. – Max.)	27.6 (25.5 – 29.6)	27.1 (25.2 – 29.4)	18.4 (15.7 – 24.9)	18 (14.2 – 24.2)	(<0.001*)
MAP (mmHg)					
Mean ± SD.	71.5^a ± 10.6	70.8^a ± 11.8	67.5^a ± 4.3	68^a ± 4	F=1.324
Median (Min. – Max.)	67.8 (62.3 – 98.3)	66.5 (59.7 – 99.7)	67 (60.7 – 75.3)	67 (62.3 – 75.3)	(0.271)
HbA1c					
Mean ± SD.	5.2^a ± 0.5	5.1^a ± 0.3	5^a ± 0.2	4.9^a ± 0.2	F=2.172
Median (Min. – Max.)	5.1 (3.9 – 6.6)	5.1 (4.6 – 5.8)	5.0 (4.5 – 5.5)	4.9 (4.6 – 5.4)	(0.097)
Total cholesterol (mg/dl)					
Mean ± SD.	148.6^a ± 15.6	140.9^a ± 17.7	139^a ± 18.5	138.9^a ± 17.3	F=1.690
Median (Min. – Max.)	148 (122 – 189)	143 (117 – 184)	139.5 (104 – 172)	140 (109 – 172)	(0.175)
HDL (mg/dl)					
Mean ± SD.	37.2^d ± 2.1	41^c ± 3.7	46.1^b ± 8.8	52.2^a ± 2.2	F=40.435*
Median (Min. – Max.)	37 (31 – 41)	41 (34 – 47)	45 (32 – 61)	52 (48 – 57)	(<0.001*)
TG (mg/dl)					
Mean ± SD.	73.4^a ± 15.2	72.2^a ± 9.2	66.2^a ± 14	65.9^a ± 11.8	F=2.292
Median (Min. – Max.)	74 (47 – 103)	71 (58 – 93)	65 (42 – 89)	65 (48 – 89)	(0.083)
LDL (mg/dl)					
Mean ± SD.	93.1^a ± 15.9	85.4^a ± 16.8	82.5^a ± 18.6	83.5^a ± 19.6	F=1.745
Median (Min. – Max.)	93 (58.8 – 122.8)	85.6 (58.4 – 125.2)	81.4 (50.2 – 119.6)	82.9 (47.2 – 119.6)	(0.163)
ESR					
Mean ± SD.	12 ± 4.6	11.1 ± 5	8.8 ± 2.4	8.4 ± 2.3	H=13.158*
Median (Min. – Max.)	13^a (4 – 16)	13^a (4 – 16)	9^b (5 – 12)	8^b (5 – 12)	(0.004*)
CRP					
Mean ± SD.	6.2^a ± 1.5	7.1^a ± 2.6	6.3^a ± 2.6	6.3^a ± 2.5	F=0.770
Median (Min. – Max.)	6 (4 – 8)	6 (4 – 12)	6 (4 – 12)	6 (4 – 12)	(0.514)
TBARS (nmol/ml)					
Normal (0 – 0.8)	18 (75.0%)	20 (83.3%)	22 (91.7%)	24 (100%)	χ^2=7.711*
Abnormal (>0.8)	6 (25.0%)	4 (16.7%)	2 (8.3%)	0 (0%)	(^{MC}p=0.038*)
Mean ± SD.	0.64 ± 0.36	0.48 ± 0.29	0.33 ± 0.28	0.20 ± 0.21	H=31.040*
Median (Min. – Max.)	0.55^a (0.15 – 1.35)	0.40^a (0.07 – 1.1)	0.22^b (0.13 – 1.32)	0.10^b (0.01 – 0.60)	(<0.001*)
Asthma controlled					
No	13 (54.2%)	–	5 (20.8%)	–	χ^2=5.689*
Yes	11 (45.8%)	–	19 (79.2%)	–	(0.017*)

SD: Standard deviation
Group 1: Overweight asthmatic; Group 2: Overweight only
Group 3: Non overweight asthmatic; Group 4:Non overweight non asthmatic (control)

off value d"0.45and with both sensitivity and specificity 93.33% and 93.33% respectively

DISCUSSION

Asthma is a problem in the lung caused by long standing inflammation and accompanied

Table 2. Comparison between asthmatics and non-asthmatics groups according to laboratory investigation

	Asthmatics (n = 48)	Non-asthmatics (n = 48)	Test of Sig.	P
HbA1C				
Mean ± SD.	5.1 ± 0.4	5.0 ± 0.3	t=0.830	0.408
Median (Min. – Max.)	5.1 (3.9 – 6.6)	4.9 (4.6 – 5.8)		
Total cholesterol (mg/dl)				
Mean ± SD.	143.8 ± 17.6	139.9 ± 17.3	t=1.098	0.275
Median (Min. – Max.)	144.5 (104.0 – 189.0)	140.5 (109 – 184)		
TG (mg/dl)				
Mean ± SD.	69.8 ± 14.9	69.1 ± 10.9	t=0.273	0.785
Median (Min. – Max.)	70.0 (42.0 – 103.0)	69.5 (48.0 – 93.0)		
LDL (mg/dl)				
Mean ± SD.	87.8 ± 17.9	84.5 ± 18.1	t=0.903	0.369
Median (Min. – Max.)	89 (50.2 – 122.8)	83.9 (47.2 – 125.2)		
CRP				
Mean ± SD.	6.2 ± 2.1	6.7 ± 2.6	t=1.044	0.299
Median (Min. – Max.)	6 (4 – 12)	6 (4 – 12)		
TBARS (nmol/ml)				
Mean ± SD.	0.49 ± 0.36	0.34 ± 0.29	U=801.50*	0.010*
Median (Min. – Max.)	0.4 (0.1 – 1.4)	0.3 (0.01 – 1.1)		

Asthmatics: Group 1 + Group 3
Non-asthmatics: Group 2 + Group 4

Table 3. laboratory investigations of controlled and uncontrolled groups

	Controlled (n = 30)	Uncontrolled (n = 18)	p
HbA1C			
Mean ± SD.	5.1 ± 0.4	5 ± 0.4	0.488
Median (Min. – Max.)	5 (4.5 – 6.6)	5.1 (3.9 – 5.5)	
Total cholesterol (mg/dl)			
Mean ± SD.	147.2 ± 17.9	138.3 ± 16	0.091
Median (Min. – Max.)	149 (110 – 189)	139.5 (104 – 169)	
TG (mg/dl)			
Mean ± SD.	71.9 ± 14.7	66.3 ± 14.9	0.217
Median (Min. – Max.)	72 (44 – 103)	64 (42 – 92)	
LDL (mg/dl)			
Mean ± SD.	91.3 ± 17.4	82 ± 17.8	0.082
Median (Min. – Max.)	93 (50.2 – 122.8)	82.4 (55.2 – 117.8)	
CRP			
Mean ± SD.	6.5 ± 2.3	5.8 ± 1.6	0.274
Median (Min. – Max.)	6 (4 – 12)	6 (4 – 8)	
TBARS (nmol/ml)			
Mean ± SD.	0.27 ± 0.11	0.84 ± 0.33	<0.001*
Median (Min. – Max.)	0.2 (0.1 – 0.6)	0.8 (0.2 – 1.4)	

with repeated attacks of abnormal breath sounds and coughing which are due to high level of oxidative stress[15]. In our study we found significant increase in the TBARS level in overweight children with bronchial asthma in relation to those who are not. Our results were similar to what To et al concluded in their study about relation between oxidative stress and obese asthmatic patients where they found that serum leptin and TBRAS were significant in overweight children with bronchial asthma than non-overweight asthmatic group[16]. Our results were also similar to Antczak

Table 4. TBARS (nmol/ml) level among the different studied groups

	Controlled		Uncontrolled		
	Overweight asthmatic (G1) (n = 11)	Non overweight asthmatic (G3) (n = 19)	Overweight asthmatic (G1) (n = 13)	Non overweight asthmatic (G3) (n = 5)	Test of Sig. (p)
TBARS (nmol/ml)					
Normal (0 – 0.8)	11 (100%)	19 (100%)	7 (53.8%)	3 (60%)	χ^2=14.760*
Abnormal (>0.8)	0 (0%)	0 (0%)	6 (46.2%)	2 (40%)	(^{MC}p=0.001*)
Mean ± SD.	0.36 ± 0.13	0.22 ± 0.06	0.88 ± 0.33	0.76 ± 0.36	H=30.680*
Median (Min. – Max.)	0.4^{b} (0.2 – 0.6)	0.2^{c} (0.1 – 0.4)	0.8^{a} (0.2 – 1.4)	0.6^{ab} (0.4 – 1.3)	(<0.001*)

Table 5. Agreement (sensitivity, specificity) for TBARS (nmol/ml) to diagnose asthmatics patients(n = 48) from non-asthmatics patients (n = 48)

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
TBARS (nmol/ml)	0.652	0.010*	0.539 – 0.765	>0.3	56.25	58.33	57.4	57.1

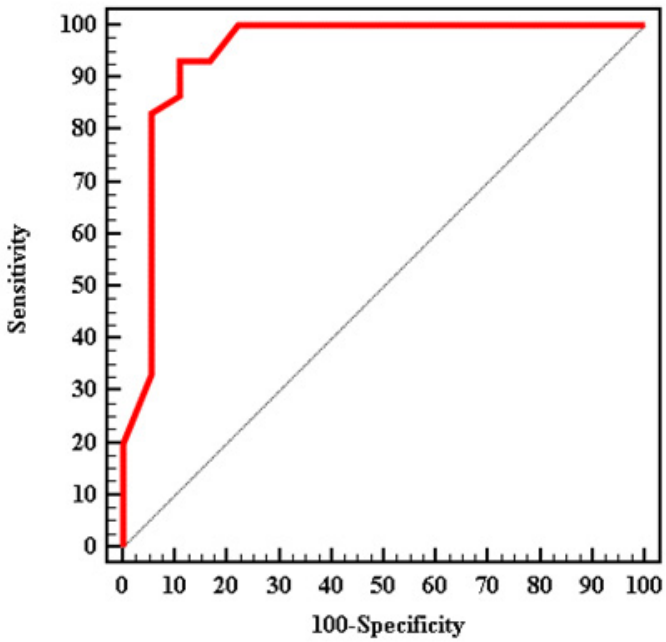

Fig. 2. ROC curve for TBARS (nmol/ml) to diagnose asthma controlled patients (n = 30) from non-asthma controlled patients (n = 18)

et al study when they found significant increase in TBRAS in asthmatic patients when compared to non asthmatic group and they concluded that detection of these markers in the exhaled air could be useful noninvasive biochemical marker of airway inflammation[17].

Although Assessment of TBRAS as an oxidative stress marker in obese asthmatic children was not clearly discussed in the literature, the role of oxidative stress biomarkers in bronchial asthma has been widely discussed by many authors as a result of its high value. Karadogan et al studied, levels of MDA, protein carbonyls (PC), and reduced glutathione (GSH) as part of oxidative markers in their study on asthmatic patients .MDA and PC were significant in uncontrolled group when compared to other groups,(18) the results that support significant increase in the TBARS level in uncontrolled Asthmatic patients when compared to the controlled one in our study. Another study supported our results conducted by Topic et al while discussing Oxidative Stress in the Childhood Asthma when they found significant increase in the level of myeloperoxidase (MPO) and percent of granulocytes in severe persistent asthma when compared with other groups of asthma[19].

Alalameey et al conducted a study to assess the role of asymmetric dimethylarginine (ADMA) , and (MDA) as oxidant indicators and serum paraoxonase pattern as an antioxidant indicator in bronchial asthma, they found that Serum levels of ADMA and MDA were suggestively higher with in severe asthmatic attacks.[20]

Scott et al., also concluded in their study that high levels of ADMA were affected by the degree of asthma prognosis.[21]

Bishopp et al conducted a study comparing fractional exhaled nitric oxide (FeNO), exhaled breath condensate nitrite/nitrate (EBC-NOx), spirometry, and serum vitamins and trace elements in asthmatic and non asthmatic children. They found significant increase in FeNO level in severely asthmatic children[22] A Saudi study was conducted among obese asthmatic children when Serum Ghrelin Levels were measured. In this study the authors found that serum ghrelin, IL-4, and IL-21 levels were statistically significant among uncontrolled children in comparison

Table 6. Univariate and multivariate logistic regression analysis for the parameters affecting abnormality TBARS (nmol/ml) (n = 12 vs. 84)

	Univariate p	#Multivariate OR (95%C.I)	P	OR (95%C.I)
Female	0.089	3.300 (0.834 – 13.052)		
Obesity	0.025*	6.053 (1.249 – 29.321)	0.541	1.785 (0.278 – 11.442)
Asthmatic	0.225	2.200 (0.615 – 7.868)		
Age (years)	0.963	1.007 (0.743 – 1.365)		
BMI (kg/m^2)	0.015*	1.278 (1.049 – 1.556)		
MAP (mmHg)	0.876	1.006 (0.938 – 1.078)		
HbA1c	0.487	1.764 (0.356 – 8.741)		
Total cholesterol (mg/dl)	0.383	1.016 (0.981 – 1.052)		
HDL (mg/dl)	0.014*	0.856 (0.756 – 0.969)	0.103	0.885 (0.763 – 1.025)
TG (mg/dl)	0.202	0.968 (0.922 – 1.017)		
LDL (mg/dl)	0.222	1.022 (0.987 – 1.059)		
ESR	0.032*	1.210 (1.016 – 1.441)	0.276	1.099 (0.927 – 1.302)
CRP	0.395	0.878 (0.649 – 1.186)		

Table 7. Agreement (sensitivity, specificity) for TBARS (nmol/ml) to diagnose asthma controlled patients (n = 30) from non-asthma controlled patients (n = 18)

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
TBARS (nmol/ml)	0.945	<0.001*	0.865 – 1.000	d”0.45#	93.33	88.89	93.3	88.9

with controlled group[23]. On contrast of our study Dut et al discovered no difference between mild and severe asthma while measuring levels of malondialdehyde and glutathione by collecting Exhaled breath condensate from the children[24]

TBARS was significant in obese asthmatic children in relation to the other groups. There was agreement that overweight children have increased amount of systemic oxidative stress,[25] with enlarged fat tissue generating proinflammatory cytokines and adipokines which cause many metabolic problems.[26] The relation between overweight and bronchial hyper reactivity is still not clear, however many hypotheses have appeared , describing the effects of inflammatory adipokines on bronchial degree of inflammation, hormonal pattern during lung growth in overweight children, bronchial remodeling in response to mechanical stresses, and genetic pleomorphism that control risk for asthma and obesity.[27] Soliman et al discussed the role of some oxidative stress biomarkers as High mobility group box 1 (HMGB1), interleukin 8 (IL-8), monocyte chemoattractant protein 1 (MCP-1), extracellular signal-regulated protein kinases 1 and 2 (ERK1/2), and urinary Hsp72 in pathogenesis of asthma in patients with increased body weight. There were significant increase in serum HMGB1, IL-8, MCP1, ERK1/2, FFAs, and H2O2 levels with urinary Hsp72 levels in patients with increased body weight with asthma in relation to other groups[28]

Shim et al found that the glycation end products (RAGE) mRNA expression was significantly higher among obese asthmatic patients than other groups in their study. They found close association of RAGE legends with hyperactivity and its prognosis as well as more RAGE up-regulation and amplification.[29] RAGE is an important factor in tumor growth development and a detector of problems with inflammation as in childhood asthma[30]. In our study we found the high oxidative stress burden with increased asthma severity during measuring TBRAS which concluded that TBRAS is a good biomarker for oxidative stress in asthmatic patients and in many other diseases. Nacítarhan et al found high MDA levels were statistically significant in diabetic patients with hyperlipidemia than those with normal lipid profile. Serum MDA quantity in the group diagnosed with diabetes and increased lipid and MDA quantity measured in urine in both diabetic groups were statistically significant when compared with those in hyperlipidemic non diabetic group.[29]. Many authors have shown in their studies higher levels of MDA in Type 1 and Type 2 diabetic patients.[30,31,32,33]

Walter et al in their analysis of the PREVENT study found that TBARS amounts were used as a good markers for cardiovascular problems in patients with controlled coronary heart problems[34]

CONCLUSIONS

Our study showed that severity of asthma depends on the level of oxidative stress as measured by TBRAS. TBRAS measurement is a good indicator of relation between bronchial hyperactivity and oxidative stress that became high with uncontrolled athma.

We also provided further proof about the importance of TBRAS in the development of asthma. Further studies are needed to discuss the role of more oxidative stress markers in bronchial asthma and obesity.

ACKNOWLEDGMENT

We d like to thanks the pediatric department Alazhar university for their kind help in doing such work.

Funding source

No fund received

Conflict of Interest

No conflict of interest**.**

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