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Asthma Severity and Serum Leptin Level in Obese Egyptian Children

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Authors' contributions

This work was carried out in collaboration among all authors. Author EFE designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript, Authors OAZ and MMA managed the analyses of the study. Author HAS managed the literature searches and contributed in writing the final manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: The relation between leptin and asthma is still unclear especially in obese children. We hypothesized that high serum leptin concentrations would also be associated with asthma in obese Egyptian children. We aimed to evaluate serum leptin concentrations in asthmatic obese and none obese children to investigate their association with asthma and degree of asthma severity.
Subjects and Methods: The study was carried out on 56 Children attended pediatric outpatient clinic of Suez Canal University hospital on Jan, 2016 to Dec 2016. They were divided into three groups (group 1) asthmatic obese children involved 16 child (group 2) asthmatic non- obese child; 20 (group 3) 20 non asthmatic child as control. Diagnosis of asthma was done according to global initiative of asthma. Serum leptin level was assessed in all study groups by ELISA.
Results: Serum leptin levels in obese asthmatic patients was 91.3±9.3 ng/ml ,while in non-obese asthmatics it was 87.8±5.6 ng/ml, finally in non-asthmatic control it was71.3±8.2 ng/ml (P value 0.175). There was positive significant correlation between serum leptin levels and asthma severity (p = <0.001). There was also significant negative association of leptin with peak expiratory flow rate results; There was also significant relation between serum leptin levels and history of allergy as

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well as family history of asthma (p = <0.001). There was significantly higher body mass index in asthmatics than non-asthmatics (p = 0.004).
Conclusion: Leptin is playing an important role in assessment of asthma severity and is the most predictive factor for asthma severity when compared to body mass index, family history of asthma and history of allergy.

Keywords: Asthma; leptin; asthma severity; body mass index.

ABBREVIATIONS

BMI : Body Mass Index;
PEFR : Peak Expiratory Flow Rate test;
ELISA : Enzyme-Linked Immunosorbent Assay;

1. INTRODUCTION

Asthma afflicts 339 million people worldwide and 8.3% of US children and is considered the most common disease of children. The annual healthcare expenditures for asthma is estimated $ 81 billion in US and EUR72 billion in Europe since it is a major reason for pediatric emergency room visits, admissions in hospitals' pediatric wards, Abstenance from schools in addition to the economic loss due to decreased parental work [1-3].

Bronchial Asthma is a chronic inflammation of the bronchial tree characterized, by completely or partially reversible airway obstruction, which may improve spontaneously or by specific therapy. Airway hyper-responsiveness is a narrowing of the airways due to a variety of stimuli, such as allergens and nonspecific triggers and infections [4].

The prevalence of asthma and allergies is increasing in both western and developing countries. Despite a large volume of clinical and epidemiological research within affected populations, the etiology and risk factors of these conditions remains poorly understood [5]. Several epidemiological studies have shown that the prevalence of bronchial asthma and obesity is increasing concomitantly worldwide among children and young adults [6]. Obesity may be associated with respiratory symptoms via cardio-respiratory deconditioning, physiological restriction of the chest wall by excess adipose tissue, or comorbidities, including gastro esophageal reflux and sleep-disordered breathing [7]. Obesity is characterized by chronic low-grade systemic inflammation. Obese adipose tissue is infiltrated by macrophages that are a source of inflammatory cytokines [8], More than 50 different adipocytokines are secreted by adipocytes. Adipocytokines are proteins that help regulate various body functions [9]. Serum leptin is pro inflammatory adipocytokine that affects both innate and adaptive immune responses, and its serum levels are markedly increased in obesity [10]. Leptin is one of the adipose tissue-derived energy-regulating hormones and a product of the obesity gene. Circulating leptin is positively correlated with body fat percentage and body fat mass. In addition to its primary effects on energy regulation, which it exerts by inhibiting food intake and increasing energy expenditure, leptin has been found to play a regulatory role within the immune system [11]. The regulatory capacity of leptin is associated not only with adaptive immunity but also with the innate system [12]. Leptin promotes the production of nitric oxide and pro-inflammatory cytokines in macrophages and monocytes [10].

The aim of this study was to evaluate serum leptin concentrations in asthmatic obese and none obese children and its association with degree of asthma severity.

What is known?

- Serum leptin is pro inflammatory cytokine that affects both innate and adaptive immune responses, and serum levels are markedly increased in obesity.
- Circulating leptin is positively correlated with body fat percentage and body fat mass.

What is New?

- Leptin is playing an important role in assessment of asthma severity.
- There is a significant relation between serum leptin levels and history of allergy as well as family history of asthma.

2. MATERIALS AND METHODS

This study is observational cross-sectional case control. This study was conducted among asthmatic children in pediatric outpatients clinic

in Suez Canal University hospital. Control group was normal healthy children. Fifty-six children were included; 20 non asthmatic children (control group) and 36 asthmatic children; 16 obese asthmatic and 20 non obese asthmatic, all aged above 3 years old. Diagnosis of asthma was done according to global initiative of asthma (GINA 2015).

Obese children were identified as children with body mass index above 95th percentile for their age according to Egyptian growth charts.

Inclusion criteria: Asthmatic children above 3 years old who did not receive steroid treatment are included in the study without injury of vital organs including heart, liver and kidney.

Exclusion criteria: children who receive treatment with steroid either by inhalation or systemic route or children with infection and severe allergic reactions are excluded from the study. The ethical committee of Suez Canal University hospital approved the study and signed informed consent of children's guardians is obtained.

Detailed history and full clinical examination was done.

2.1 Pulmonary Function Test

It was done by peak Expiratory Flow Rate test (PEFR) for children above five years old.

2.2 Leptin Assessment

Five ml blood samples was collected by a skilled and qualified technician at the outpatient clinic around 8 a.m. in the morning following an overnight fast. After collection, the blood samples was centrifuged for 10 minutes and serum leptin stored at −80 C. The materials used for collection was disposable, adequately labeled, and of recognized quality. Leptin levels measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions and standard guidelines.

Statistical analysis was performed using SPSS for Windows statistical package, version 20. (SPSS, Inc., Chicago, Ill., USA). Data were expressed as mean ± SD. Student's t test, Mann-Whitney U test and χ^2 test were used for comparing mean values. A p value <0.05 was considered statistically significant.

3. RESULTS

3.1 Demographic Data

This study was carried out on fifty-six children divided as; 20 non asthmatic children (control group) and 36 asthmatic children; 16 obese asthmatic and 20 non obese asthmatic, all aged above 3 years old, the mean BMI in was 21.3±5.8 and 16.6±2.4 in asthmatic and non-asthmatic groups respectively. The mean age of asthmatic group was 7.3±3.3 while it was 8.5±3.6 in non-asthmatic group, all these data are summarized in Table 1.

Serum leptin was significantly higher in asthmatics than non-asthmatics (p=<0.001), but there was no significant relation between serum leptin in obese asthmatic and non-obese asthmatic (p=0.175) as shown in Table 2.

Relation of serum Leptin and degree of asthma severity: Table 3 shows significantly higher serum leptin in severe asthmatics 97.6±8.5, than moderate 89.3±4.6 and mild asthmatics 82.0±3.2 (p =<0.001) respectively.

Table 1. Socio demographic parameters of study groups

	Asthmatic (36)	Non-asthmatic (20)	P value	Obese asthmatics (16)	Non-obese asthmatics (20)	P value
Age (years)	7.3±3.3	8.5±3.6	0.201			
Body weight	33.0±15.5	30.8±14.5	0.584			
Height	122.0±19.8	132.3±21.4	0.081			
BMI	21.3±5.8	16.6±2.4	0.004*			
Sex						
Males	17(47.2%)	11(55.0%)	0.577			
Females	19(52.8%)	9(45.0%)	0.201			
Serum leptin	89.3±7.6	71.3±8.2	<0.001*	91.3±9.3	87.8±5.6	0.175

data was presented as means ± SD or No. and %
** Statistically significant p <0.05; ≠ OR for sex (male/female)*

Table 2. Relation of serum leptin and degree of asthma severity

	Asthma severity			P value
	Mild (9)	Moderate (19)	Severe (8)	
Serum leptin	82.0±3.2	89.3±4.6	97.6±8.5	<0.001*

Table 3. Relation between serum leptin levels and history of allergy

	Serum leptin (Mean ± SD)		P value
	Positive	Negative	
History of allergy	87.7±9.0	79.5±12.2	***0.019**
Family history of asthma	91.2±7.4	75.7±9.7	**0.001>.***

Table 4. Comparison between serum leptin in study groups

Serum leptin	Group		P value			P value
	Asthmatics (36)	Non-asthmatics (20)		Obese asthmatics (16)	Non-obese asthmatics (20)	
	89.3±7.6	71.3±8.2	<0.001*	91.3±9.3	87.8±5.6	0.175

** Statistically significant at p<0.05*

Table 5. Relation of clinical parameters of asthmatics and asthma severity

	Asthma severity			P value
	Mild (9)	Moderate (19)	Severe (8)	
Age (years)	7.7±3.6	7.5±3.6	6.5±2.8	0.776
Body weight	34.0±11.6	34.0±18.5	29.6±12.5	0.745
Height	126.1±21.1	122.2±20.3	117.1±18.8	0.666
BMI	21.3±6.0	21.5±6.2	20.9±5.5	0.995
Sex				
Males	6(66.7%)	7(36.8%)	4(50.0%)	0.338
Females	3(33.3%)	12(63.2%)	4(50.0%)	
History of allergy	3(33.3%)	8(42.1%)	5(62.5%)	0.503
Family history of asthma	2(22.2%)	14(73.7%)	8(100.0%)	0.002*
Serum leptin	82.0±3.2	89.3±4.6	97.6±8.5	<0.001*
PEFR	146.1±50.9	140.2±67.9	151.1±62.9	0.824

*data was presented as means ± SD or No. and %; * Statistically significant p <0.05*

There was positive significant correlation between serum leptin levels and asthma severity (Correlation Coefficient was 0.862* and p value was <0.001) while it is demonstrated a significant negative association of leptin with PEFR results r=-0.468 and p<0.001.

Relation between serum leptin levels and history of allergy: Table 2 shows a significant relation between serum leptin levels and history of allergy (p =0.019) as well as family history of asthma (p = <0.001).

Relation between body mass index and asthma severity: Table 3 shows a significant moderate positive correlation between body mass index and asthma severity (rho=0.334, p=0.012). Table 4 Show Serum leptin was significantly higher in asthmatics than non-asthmatics (p=<0.001)

There was significant negative association between Peak Expiratory Flow Rate results and asthma severity. r=-0.427and p=0.001.

ROC curve of serum leptin for diagnosis of severe asthma showed serum leptin was 91.5% accurate in diagnosis of severe asthma (AUC=0.915, p<0.001). At cutoff value of 75.5, serum leptin was shown 100% Sensitivity and 75% Specificity for diagnosis of severe asthma.

4. DISCUSSION

Leptin is an obesity gene product derived from adipocytes and activates proinflammtory adipocytokines including tumor necrosis factor α, interleukine-6 and interferon-γ.

This study showed no statistically significant difference between the two study groups in terms

of socio demographic characteristics (age, body weight, height and sex) (p >0.05).

In addition, the current study reported a significant difference between asthmatic and control groups in terms of BMI (21.3±5.8, 16.6±2.4 respectively, p = 0.004). These findings are similar to those reported by Black et al who also found a significant difference between asthmatics and control groups in terms of BMI [13]. Furthermore, a recent meta-analytic study of 18 studies which included 73,252 children reported that overweight or obesity was a significant risk factor for asthma in obese children [14].

However our study revealed no statistically significant difference in BMI between obese and non-obese asthmatic children. The present study showed that serum leptin levels of asthmatic children (89.3±7.6 ng/ml) were significantly higher than those of healthy control (71.3±8.2) p-value was <0.001. This coincides with the study done by About Yousif, et al. who found a statistically significant difference in serum leptin values between asthmatics and controls being higher in asthmatics regardless to the body weight (p=0.034) [15] and also coincides with another two studies stated that even after controlling of body mass index, leptin levels were increased in asthmatic children compared to non-asthmatic children [16,17] (Table 5).

Our study showed that there was no significant difference between serum leptin in obese asthmatics and non-obese asthmatics p=0.175 and this is consistent with results reported by Shore, et al. who also found no significant difference between the two groups (p > 0.05) [18]. It was also reported by another study which demonstrated that no differences in leptin or adiponectin levels in obese and non-obese children with asthma [19].

As regard to BMI, the present study showed a significant positive correlation of leptin and BMI (r= 0.434, p=0.001) (Table 6). This result is similar to the results reported by several researchers [20,21]. Yosif, et al. suggested that BMI is the main determinants for the variations of leptin [22]. As demonstrated by French Epidemiological Study on indirect effects of leptin on Genetics and Environment of Asthma EGEA revealed that leptin partially mediated the association between obesity and persistent asthma over time [23]. A recent longitudinal study used new mediation analysis to detect the direct and indirect effects mediated by leptin in asthma development confirmed the odds ratio of direct effect were 1.59 (95% CI: 0.95-2.97), 2.06 (1.06-4.00) and 3.25 (1.01-9.41), respectively while the indirect effect mediated by leptin odds ratio were 1.68 (1.09-2.46), 1.55 (0.99-2.57) and 1.99 (0.94-4.83), respectively [24]. Leptin mediated its effects by augmenting phagocytic function.

Table 6. Socio demographic data of Asthmatic obese children

Age in year	Weight(kg)	Height(cm)	BMI	sex	Asthma severity
10	47	130	27.8	female	Mild
5	34	14	26.2	Male	Mild
11	36.5	120	25.3	Female	Moderate
5	28	103	26.4	Female	Moderate
4	31	107	27.1	Male	Mild
13	66	152	28.6	Female	Moderate
8	45	126	28.3	Female	Moderate
7	37	117	27	Male	severe
6	37	112	29.5	female	Moderate
10	47	134	26.2	Male	Moderate
9	50	133	28.3	Female	Severe
4	25	97	26.6	Female	Severe
9	43	122	28.9	female	Mild
3.5	25	98	26	Male	Moderate
10.5	58	141	29.2	Female	Moderate
15	80	162	29.7	Female	moderate

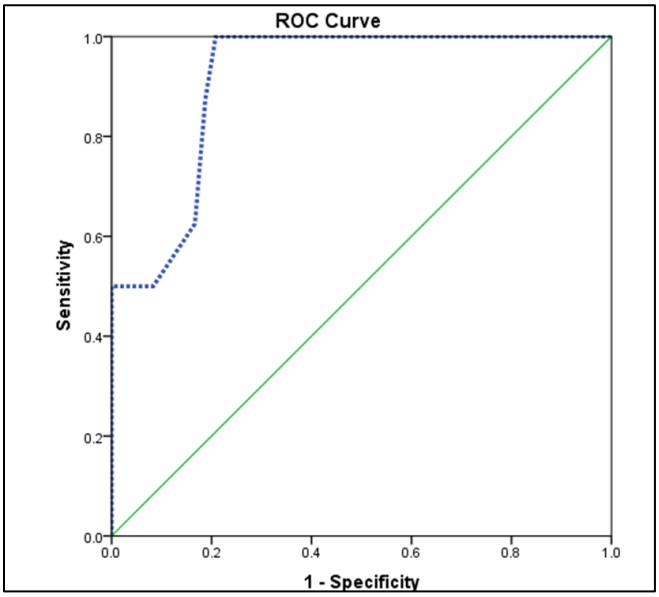

Fig. 1. ROC curve of serum Leptin for diagnosis of asthma severity

proliferation and alternation of macrophages and consequently led to increased secretion of proinflammatory cytokines. The latter include tumor necrosis factor α, reactive oxygen species and interleukin 6 [25].

Our study results showed that there was significantly negative correlation between leptin and PEFR results in total asthmatic patients (r=-0.468 and p=0.001). This result agreed with the result of Sin and Man work who also reported a negative correlation between serum leptin levels and PEFR in asthmatic patients (r=-0.521and p=0.001) [26].

Our study also showed significant relation between serum leptin levels and history of allergy (p=0.019) as well as family history of asthma (p= <0.001). The positive correlation between history of allergy and serum leptin level is consistent with these results reported by Samra, et al. as there was a positive correlation between leptin levels and history of allergy (p=0.0058) [27].

Concerning the severity of asthma, this study showed that the mean ± SD of serum leptin in moderate asthmatics (89.3±4.6 ng/ml) was significantly higher than that of mild asthmatics (82.0±3.2 ng/ml) p< 0.001. These results were in accordance with those reported by the American College of Allergy, asthma and immunology study [28], that linked serum concentration of leptin to disease activity and severity, patients with intermittent asthma had value of 8.9 ng/dl, those with mild persistent asthma had levels of 14.5 ng/dl and moderately persistent asthma patients had 18.9 ng/dl with P-value less than 0.05. Shore et al. suggested that increase serum leptin can increase airway hyperresponsivness and exacerbate asthma [29].

Our results showed that the sensitivity of serum leptin for diagnosis of severe asthma showed serum leptin was 91.5% accurate (P <0.001). At cutoff value of 75.5, serum leptin was shown 100% Sensitivity and 75% Specificity for diagnosis of severe asthma. These findings were similar to those reported by Tanju et al who reported 89% accuracy of serum leptin levels in severe asthma (P <0.001). Our results suggest that leptin is playing an important role in diagnosis and determining the severity of asthma.

The study showed also that leptin is the most predictive factor for severity of asthma when compared to body mass index, family history of asthma and history of allergy which has low significant prediction for severity of asthma.

5. CONCLUSION

Asthma in obese children is significantly correlated with serum leptin levels and BMI. So, high leptin levels and BMI may serve as markers of asthma severity in obese children as well as potential future therapeutic targets in the era of advanced bionanotechnology.This approach can be possible via targeting vital cell signaling pathways by novel ligands that act as agonists or antagonists for crucial adaptor molecules in asthma pathogenesis mediated by leptin such as

Parathyroid-hormone-related protein (PTHrP) and prostaglandin E2 (PTHrP/PPARγ) signaling pathway inhibitors.

6. FUTURE RESEARCH DIRECTIONS

Due to heterogeneity of obesity related asthma in children and its multifactorial nature of the disease with genetic-environmental interactions, it is difficult to find out precise markers. However, emerging novel biomarkers for severe asthma using multi-omics technologies such as proteomics, epigenetics, transcriptomics, metagenomics, gut microbiome and untargeted metabolomics is a promising approach. Novel innovative advances in quantum computational sciences, biostatistics and molecular bioinformatics of asthma are needed for appropriate phenotypic subclassification and searching for more precise future digital biomarkers and enabling progress of precision medicine for asthma.

CONSENT

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

ETHICAL APPROVAL

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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