Relationship between Serum Levels of Resistin and Leptin and severity of childhood Asthma

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Abstract: Background; Resistin and Leptin are protein mediators secreted by adipose tissue involved in the regulation of inflammation and allergic responses and suggested to affect the risk of asthma, this study aimed to investigate the role of these adipokines in bronchial asthma and correlate their levels with the severity of asthma
Methods ;Sixty child with mild and moderate asthma and another 20 healthy control were included in the study and subjected to; full clinical examination, Anthropometric measurements, Pulmonary function test CBC and assay of serum level of Leptin and Resistin using ELISA**. Results**; the study showed a highly significant increase in serum level of resistin and leptin in all asthmatic children compared with the level in the control group (p<0.000). Also there were significant higher levels in mild and moderate persistent asthma compared with control group (p <0.001) while insignificant higher level in mild intermittent asthma compared with control (p >0.05). There were significant differences among level of serum resistin and leptin among asthmatic groups with higher level in the more severe groups (p <00.1). In all asthmatic children, there was significant positive correlation between serum level of resistin and leptin and PBE count (r=0.83) while significant negative correlation with FEV1 and PEF (r=-0.89 and 0.88 respectively), but there was insignificant positive correlation between serum level resistin and the serum level of IgE in all asthmatic children (p <0.1). **Conclusions;** High resistin and leptin levels suggesting that these adipokines may be a marker in asthma and associated with poor lung functions suggesting that the link between adipokines and severity of asthma. Further studies are needed to understand the role of resistin and leptin in the pathogenesis of, and more importantly, in predicting treatment responses in asthma.
[Abdel hakeem Abdel mohsen and Emad Allam. **Relationship between Serum Levels of Resistin and Leptin and severity of childhood Asthma.** *J Am Sci* 2012;8(11):635-641]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 94

Keywords; bronchial asthma, adipokines, resistin, leptin

1. Introduction

Asthma is a chronic inflammatory airway disease characterized by cough, chest tightness and wheezing, and it is associated with reversible or variable airway obstruction. However, the diagnosis and follow-up of the disease are currently based on symptoms and lung function measurements rather than on assessing the underlying inflammatory process [1]. Adipokines like leptin and resistin are protein mediators secreted by adipocytes and macrophages within the adipose tissue [2]. Leptin and resistin are usually pro-inflammatory [3]. Leptin levels increase in obesity [4] and leptin has therefore been suggested to belong to the factors explaining the relation between obesity and asthma. Some studies suggest that leptin affects asthma also independently of body mass index (BMI) [5]. Resistin is a newly identified adipocyte secreted hormone belonging to a cysteine-rich protein family (6) known as resistin-like molecules (RELMs). Variety of human tissues showed that human resistin was expressed at the highest level in bone marrow followed by lung (7) Placental tissue (8) and pancreatic islet cells (9). Resistin contribute to the development of obesity-mediated adverse effects on glucose and lipid metabolism. It is also likely that some of these adipokines are specific fat-derived hormones that affect human energy homeostasis and insulin action and may be involved in hemopoiesis and immunity (10, 11) Several studies showed that resistin may also play a pivotal role in inflammation and process of inflammation-related diseases (12).

The aim of this study was to evaluate the levels of Resistin and leptin in asthmatic children and correlate their levels with the lung functions and severity of asthma

2. Patients and Methods

This cross section study was conducted at the outpatient pulmonology clinic, department of pediatrics, Minia University, during the period from January 2011 till April 2012. Sixty child with mild and moderate asthma included in the study. They were diagnosed according to Global Strategy for Asthma Management and Prevention Classification [13]. In addition 20 healthy children cross matched age and sex were taken as control group.

The asthmatic children who were divided into 3 groups depending on severity of asthma;

Group (1*):* included 23 children (14 males and 9 females) with mild intermittent asthma their age ranged from 7-11.5 years.

Group (2): included 22 children (12 males and 10 females) with mild persistent asthma, their age ranged from 6-13 years.

Group (3*):* included 15 children (7 males and 8 females) with moderate persistent asthma, their age ranged from 8-13 years

Group 4: included 20 apparently healthy children (12 males and 8 females) as a control group, their age ranged from 7-12.5 years.

Exclusion Criteria:

1- Children who receive treatment with steroid either by inhalation or systemic.

2- Children with systemic diseases.

3- Peak expiratory flow rate more than 90%

Methods: both patients and control were subjected to

- Detailed history was taken and full clinical examination was performed. Anthropometric measurements were assessed: The heights were measured by using a wall-mounted Harperder stadiometer (Haltain Limited. Crymych. Dyfeed. U K). Weight was determined in low clothes by using calibrated electronic scale (Seca Hamburg. Ger) .Body mass index (BMI) was calculated as weight (kg)/height (m2).
- Pulmonary function test was done by peak expiratory flow rate test (PEFR). This test was made by a peak expiratory flow monitor which is a small handheld device with a mouth piece at one end and a scale with a moveable indicator (small plastic arrow).

The Test Was Performed as Follow:

- Patient breathed in as deeply as possible and Blow into the instrument's mouthpiece as hard and fast as possible. This was done 3 times, and we recorded the highest flow rate. Predicted Values of PEFR were determined by age and height

Laboratory investigations; complete blood picture and serum IgE level were done for all asthmatics who attend to the clinic. In addition serum leptin and resistin concentration was estimated to all asthmatic and control groups.

- Blood samples obtained and centrifuged at 2,500g for 15 min at 4°C within 30 min of collection, and the serum obtained was stored at –70°C until analysis.
- Leptin assay; were done by biosource leptin ELISA kits with catalogue number KAF2281: 96 determinations. It is an immunoenzymometric assay for the quantitative measurement of human leptin in serum and plasma.

•Resistin assay; Serum resistin concentration was measured by using a sandwich enzyme-linked immunosorbent assay (ELISA, Phoenix Pharmaceutical, Inc, Belmont, CA, USA) as previously reported .7 Intra- and inter-assay coefficients of variation were 3.4 and 6.3%, respectively.

Statistical Analysis:

The results were expressed as Mean±SD. *t*-test, ANOVA with Post-Hoc of scheffe's test were used to compare 2 or more groups of the study. Linear correlation was used for detection of correlations among groups.

3. Results

Table (1) summarizes the clinical and laboratory characteristics of the studied groups. Thirty three them were boys, 36.6% had positive parental history of asthma and 25 %of asthmatic children had history of atopy also it showed that there were a highly significant increase in serum levels of resistin and leptin in all asthmatic children compared with the control group (p<0.000). There were significant higher level of PBE count and IgE (<0.000) than the level of the control group. There were highly significant decrease of percentage of predicted of normal of FEV_1 and PEF (<0.000) compared with control group. Also there were no significant differences between asthmatic and control groups as regard to age, weight, and height and body mass index.

Table (2) showed that there were significant differences of serum resistin and leptin levels among the studied groups (p <0.001) except between groups 1 and 4 showed insignificant difference (p >0.05); the levels were higher in asthmatics than control and increasing with severity of asthma. Also, there were significant differences of PBE count levels among the 4 groups (0.001) with higher level in asthmatic groups than control and increase in more severe asthmatic groups. There were significant higher serum levels of IgE in each of asthmatic groups compared with control (p <0.01) while there were insignificant differences among the groups of asthmatic children (>0.05). In addition, there were significant differences among percentage of predicted normal of FEV1 in the studied groups (p <0.001) with lower percentage in asthmatics group than control and decrease with severity. There were significant differences among percentage of predicted normal of PEF in the studied groups (p <0.001), except between group 1 and group 2 which was insignificant (p>0.05) with lower level in asthmatics group than control and decrease with severity.

Table (3) and figure (1) showed a positive correlation between serum level resistin and PBE count in all asthmatics (r=0.83). There was insignificant positive correlation between serum resistin levels and the serum levels of IgE in all asthmatic children (r=0.22). Also there were negative correlations between serum resistin level and FEV_1 and PEF (r=-0.88, -0.89 respectively).

Table (4) and figure (2) showed a positive correlation between serum level leptin and PBE and

IgE count in all asthmatics (r=0.78, 0.509 respectively).Also there were negative correlations between serum leptin level and FEV_1 and PEF (r=-0.34, -0.65 respectively).

Table 1: Clinical characteristics and laboratory findings of the patients and control

Data	Asthmatic children N=60	Controls N=20	*p* -value
Age: Range Mean ±SD	7-12.5 9.4±1.5	7.5-12.5 9.7±1.5	0.31
Sex: Male Female	33 27	12 8	0.35 0.32
Weight - Kg - Weight/age percentile	30.8±8 54.3±30.6	30.3±6 44.6±31.4	0.19 0.16
Height: Cm Height/age percentile	133±10 38.6±24.7	134±8 46±30.4	0.30 0.26
BMI: Value (wt/m²) BMI percentile	17.3±2.5 52.5±34.3	17±1.9 55.6±26.6	0.42 0.37
Positive family history of asthma	22 (36.6%)	-	
Positive history of atopy	15 (25%)	-	
Serum resistin (ng/ml)	10.02 ± 3.81	4.16 ± 1.18	0.0000**
Serum leptin (ng / ml)	4.92 ± 0.91	1.48 ± 0.38	0.001**
PBE count (cells/µl)	450±110	154±68	0.001**
Serum IgE level (IU/ml)	228±104	119±58	0001**
% of FEV_1 predicted normal	80.2±5.9	99.1±0.S82	0000**
% of PEF predicted normal	80.4±4.6	99.2±0.78	0000**

BMI= body mass index PBE= peripheral blood eosinophils
FEV= forced expiratory volume PEF=peak expiratory flow rate ** Highly significant

Table 2: Laboratory findings and pulmonary functions among studied groups

	Group I N=23	Group II N=22	Group III N=15	Group IV N=20	*P* values			
					Grou I vs Group IV	Group II vs Group IV	Group III vs Group IV	Group I vs Group III
Serum Resistin (ng/ml)	6.03±1.75	9.14±2.86	12±3.9	5.16±1.19	>0.05	<0.001	<0.001	<0.001
Serum leptin (ng/ml)	2.2 ± 0.85	4.8 ± 0.94	5.32 ± 0.71	1.48 ± .38	>0.05	<0.001	<0.001	<0.05
PBE count (cells/µl)	366±58	433±102	525±29	154±68	<0.05	<0.001	<0.001	<0.01
Serum IgE level IU/ml	202±100.8	229.6±107.8	223±110	119±58.4	<0.05	<0.001	<0.001	<0.01
% of FEV1 predicted normal	88.9±2.7	82.5±1.7	72.8±9.7	102.6±9.8	<0.01	<0.001	<0.001	<0.05
% of PEF predicted normal	86.7±3.7	85.9±3.8*	72.8±9.7	72.8±9.7	<0.01	<0.001	<0.001	<0.01

Table (3): Correlation between serum resistin levels and each of PBE, serum IgE levels, and pulmonary functions of asthmatic children

Parameter	Serum Resistin levels	
	R	*p*
PBE count	0.83	0.0001
Serum IgE level	0.22	0.1
% of FEV1 predicted normal	-0.88	0.0001
% of PEF predicted normal	-0.89	0.0001

Table (4): Correlation between serum leptin levels and each of PBE, serum IgE levels, and pulmonary functions of asthmatic children

Parameter	Serum leptin level	
	R	*p*
PBE count	0.78	0.01
Serum IgE level	0.509	0.015
% of FEV1 predicted normal	-0.34	0.04
% of PEF predicted normal	-0.65	0.01

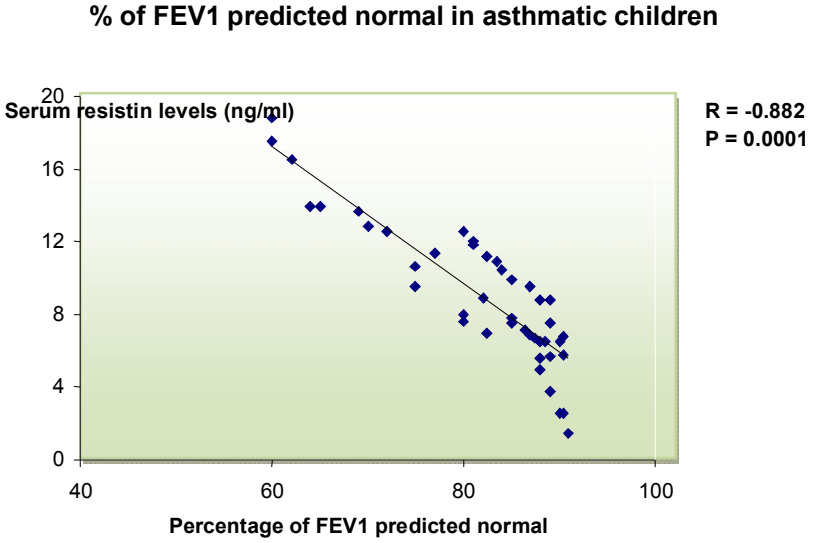

Figure 1: Correlation between serum resistin levels and

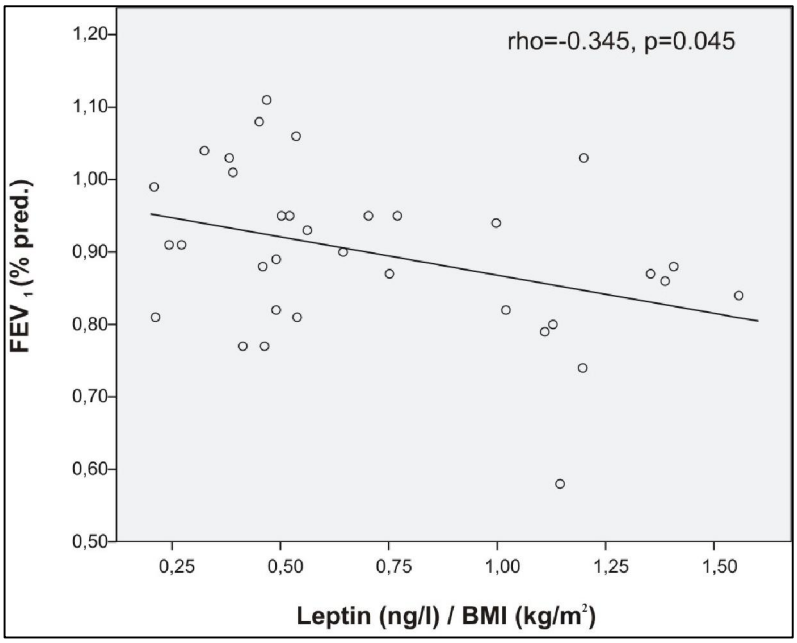

Figure 2-Correlation between serum leptin level and FEV1 in asthmatic children

4. Discussion

Resistin and leptin are protein mediators secreted by adipose tissue and have been involved in the regulation of inflammation and allergic responses, and suggested to affect the risk of asthma especially in obese patients [14]

This study was aimed to determine the serum levels of resistin and leptin in asthmatic children

compared with controls and their relationship with other parameters in asthmatic children. In our study we found insignificant statistical differences between asthmatic children and control as regard; weight, height, BMI, weight for age percentile, height for age percentile, weight for height percentile and BMI percentile Also they were insignificantly differ among the asthmatic children (p value>0.05)

There was a significant higher serum PBE count in all asthmatic children and in each group of asthmatic children when compared with the control group. Also PBE count significantly higher in more severe asthmatic groups. There were significant decrease of percentage of FEV1 and PEF predicted value in asthmatic groups with lower in more severe groups. Serum IgE levels were significantly higher in all asthmatic children and in each of the three groups of asthma compared with that of the control group but there were no significant differences among the asthmatic groups.

In the present study, serum level of resistin is significantly higher in all asthmatic children compared with the level in the control group. There were insignificant increase in the level of resistin in asthmatic children with mild intermittent asthma (group 1) compared with that of the control (p >0.05), while there were significant higher level of serum resistin level in children with mild persistent (group II) and moderate persistent asthma (group III) than the level in the control group (p <0.001).(Tab.,2)

These results in agreement with Kim *et al.,* ***(15)*** al who found significant increase in serum level of resistin in asthmatic children than the levels in the control group. Also who documented that the plasma resistin level is significantly higher in asthmatic adults than the level in their control group. However, Arshi *et al., (16)* did not find any differences in resistin levels between pediatric patients with asthma and healthy children

Also we found that there were significant increase in serum resistin levels among the asthmatic group with higher level in moderate persistent asthma than both mild persistent and mild intermittent asthmatic groups and higher in mild persistent asthma than in mild intermittent asthma.. (p <0.001) Also there were reverse correlations between serum resistin levels and the percentage of predicted normal of both FEV1 and PEF; these results indicate that the resistin level increases with increasing severity of asthma.

These results agree with those of Larochelle *et al.,* (17) who found that the plasma resistin level is significantly higher in asthmatic adults increase with the increase of frequency of symptoms of asthma in adult patients diagnosed as moderate to severe asthma.

In the present study, there was a positive correlation between serum levels of resistin and the severity of asthma and PBE count as an inflammatory marker of asthma, may suggest that resistin is more than a simple marker of asthma and it may play a role in systemic inflammatory process in asthmatic children. This may be explained by the finding that resistin is an endogenous agonist of Toll-like receptor 4 (TLR4) which leads to activation of various genes involved in asthmatic inflammation through NF-kB pathway [18]. Accordingly, we found here that resistin was able to enhance the production of proinflammatory cytokines IL-6 and TNF-α in human macrophages. Also, the expression of resistin itself has been reported to be enhanced by inflammatory factors like IL-1, IL-6, TNF-α and LPS by an NF-κB dependent manner [19,20] . Therefore high resistin levels may reflect an asthmatic phenotype characterized by increased NF-κB activity [21] .

In the present study, asthmatic children had level of IgE higher than the upper limit of the normal level matching age and sex. We found that there were significant higher levels of IgE in all asthmatic children as well as each of the three groups of asthmatic children compared with the control group while there were insignificant differences among the serum IgE level in the three groups of asthma. There was insignificant positive correlation between serum resistin level and serum IgE level in all asthmatic children. This may indicate that resistin has no role in allergic asthmatic children.

Leptin is a proteohormone that is mainly produced by white adipocyte and to a lesser extent by the placenta to act primarily through specific receptors at the hypothalamus; It decreases the appetite and increases energy expenditure[22]. Leptin receptors also exist in

human lung tissues [23]. Recent observations suggest the presence of an interaction between leptin and inflammatory system whereas there is no adequate knowledge about the role of leptin in atopic state such as asthma, although there is evidence of positive association between asthma and obesity [24]

The present study showed that leptin levels in asthmatic children were significantly higher than those of healthy control (p- 0.001). This in agreement with Abou Yousif *et al.,*[25] who proved a statistically significant difference in serum leptin value between asthmatics and controls being higher in asthmatics regardless to the body weight. Also Fumitake *et al.,*[26] investigated the relationship between serum leptin concentration and bronchial hyperresponsiveness (BHR), he observed a significant association between serum leptin concentration and BHR (p=0.038). This may explain that leptin affects asthma through its stimulation to mast cells and thus magnify airway hyperresponsiveness to allergen[24]. Increased leptin level inhibits immune response and

may play a role in asthma by regulating T-cell responses, polarizing Th cells toward a Th1 phenotype also the production of proinflammatory mediators such as tumor necrosis factor (TNF), interleukins (IL6 and IL12) which are markedly increased when exposed to leptin[27) *Xiao-Mei et al.,* [28] concluded that leptin might be involved in the pathogenesis of asthma in children and TNFá might be a pathway in the process of leptin induced inflammation.

According to the severity of asthma, this study showed that serum leptin in moderate persistent asthma was significantly higher than that of mild intermittent and mild persistent asthma $p = 0.0001$. These results were in accordance with those obtained by the American College of Allergy, asthma and immunology [29] who linked serum concentration of leptin to disease activity and severity, patients with intermittent asthma had a lower value of leptin level compared to those with persistent and moderate persistent asthma (p -value less than 0.05). Also Shore *et al.*[30] suggested that increase serum leptin can increase airway response and exacerbate asthma.

Our study showed that there was a positive correlation between level of leptin and PBE count (r=0.78). This result was similar to the result of Ciprandi *et al.,*[31] who found that there is significant association between serum leptin level and eosinophil count in males . Human eosinophils express leptin surface receptors under *in vitro* and *in vivo* conditions. It delays apoptosis of mature eosinophils *in vitro*. The antiapoptotic effects of leptin were concentration dependant so leptin is a survival cytokine for human eosinophils; a finding with potential pathologic relevance in allergic and parasitic disease.

Another aspect of this study showed the correlation between concentration of serum leptin and some parameters in asthmatic children such as immunoglobulin E (IgE) levels and peak expiratory flow rate (PEFR). The present study showed that there was a positive correlation between serum leptin level and IgE levels (r=0.509) and (p=0.015). These results coincided with those obtained by Jung *et al.,*[32] who proved that log total IgE levels were greatly associated with log leptin level (p=0.01). On the other hand Erel *et al.,* [33] found no association between leptin level and total IgE level (p>0.05). This study found there was significant negative correlation between leptin and peak expiratory flow rate results in total asthmatic patients (r=-0.65 and p =0.01). This result agreed with the result of Sin,[34] who determine the relationship between circulating leptin levels and forced expiratory volume in one second (FEV1) values. He found that serum leptin levels changed along the FEV1 gradient, so that individuals with impaired lung function have raised serum leptin levels. Hansel *et al.,*[35] identified significant associations between lung function decline and 21 single nucleotide pleomorphism in leptin receptors (p <0.05).

Our study has the limitation that there were no patients with severe lung disease and so the relation between severe lung disease and resistin and leptin remained unexplored.

Conclusion

The study concluded that serum resistin and leptin levels increase in asthmatic children with increasing with severity. Also its level positively correlated with PBE count and reverse correlated with percentage of predicted value of FEV1 and PEF. These concluded that resistin and leptin may play a role in systemic inflammatory cascade in asthmatic children. We recommended more studies to confirm the role of resistin and leptin in asthmatic children and to detect its role in airway inflammatory reactions in asthma and other allergic diseases

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10/12/2012