ORIGINAL ARTICLE

Serum resistin levels are elevated in schoolchildren with atopic asthma

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Abstract

OBJECTIVES: There are limited data on the role of adipokines in atopic asthma.
DESIGN AND SETTING: To determine serum levels of resistin in asthmatic children in relation to body weight, asthma severity and gender, serum resistin (RES) levels were measured using ELISA in 89 asthmatic children (61 boys and 28 girls, aged 7.0–17.0 years) and in 33 healthy children. Among examined asthmatics 59 (19 girls and 40 boys) had normal weight (ANW) and 30 (9 girls and 21 boys) were obese (AO).
RESULTS: The mean serum levels of resistin were significantly ($p<0.01$) higher in all non-obese asthmatic children (4.11±0.1 ng/mL) than in healthy children (3.83±0.1 ng/mL). After stratifying by gender only ANW boys and AO boys had significantly higher RES levels than boys from control group. Both AO (4.4±0.2 ng/mL) and ANW girls (4.38±0.2 ng/mL) as well as girls from control (4.09±0.1) group showed significantly higher mean RES serum concentrations than boys from corresponding groups (3.99±0.1 ng/ml, 3.83±0.17 ng/ml and 3.44±0.06 ng/ml, respectively). No relationship between examined adipokine levels and asthma severity, spirometric parameters, degree of allergic sensitization, BMI, BMI-SDS was stated.
CONCLUSION: Increased serum RES in children with atopic asthma suggest that this adipokine may be implicated in its pathogenesis.

INTRODUCTION

Several cross-sectional, case-control, longitudinal, and weight intervention studies demonstrated that obesity is associated with asthma in both adults and children. However, the exact mechanisms for the association between obesity and asthma are not known. The immunologic pathway involves a possible role for pro-inflammatory and anti-inflammatory adipokines produced by adipose tissue (Beckett *et al.* 2001, Beuther *et al.* 2007, Castro-Rodríguez *et al.* 2001, Figueroa-Muñoz *et al.* 2001, Jartii *et al.* 2009).

Although adipose tissue produces over 100 adipokines, most reports focused on the role of

pro-inflammatory leptin and anti-inflammatory adiponectin, which may affect asthma. However, recent data are inconclusive regarding the independent association between serum leptin or adiponectin levels and the risk of asthma (Nagel *et al.* 2009, Sood *et al.* 2006, Sutherland *et al.* 2009). Some findings suggest that leptin and adiponectin might be involved in the pathogenetic relationship between obesity and allergic sensitization and asthma in humans (Nagel *et al.* 2009, Sood *et al.* 2006), but the other studies do not confirm this hypothesis (Jartii *et al.* 2009).

Another adipokine, resistin (RES), received its name from the original observation by Steppan *et al.* (2001) who reported its role in inducing insulin resistance in mice. It should be noted here that in human insulin resistance may be associated with an increased risk of asthma-like symptoms development (Husemoen *et al.* 2008).

Resistin (also known as ADSF – *adipocyte-specific secretory factor*, FIZZ3 –*found in inflammatory zone family*) a 12.5-kDa protein, containing 108 amino acids in the form of pre-peptide, was identified in 2001. This transcript overexpressed in preadipocytes (precursors of fat cells) has been described by several groups of researchers as a new factor secreted by adipose tissue homologous to proteins secreted during inflammatory processes (Steppan *et al.* 2001, Holcomb *et al.* 2000, Meier *et al.* 2004).

Resistin belongs to the family of resistin-like molecules (RELMs). So far, four members of this family have been identified: RELM-α (FIZZ-1), RELM-β (FIZZ-2), resistin (FIZZ-3) and RELM-γ (Meier *et al.* 2004 , Steppan & Lazar, 2004).

RELM-α (FIZZ-1) was initially discovered in the bronchoalveolar lavage fluid of mice with allergic pulmonary inflammation (Mishra *et al.* 2007). Expression of RELM-α (FIZZ-1) has been shown to be elevated in response to pulmonary inflammation (Jartii *et al.* 2009, Kim *et al.* 2008). Relationship between adipokines and manifestations of childhood asthma.

RELM-β (FIZZ-2) has a role in promoting airway inflammation and lung remodeling in mouse lungs by inducing dose-dependent leukocyte accumulation, goblet-cell hyperplasia, and perivascular and peribronchial collagen deposition (Mishra *et al.* 2007).

RELM-β (FIZZ-2) also potentially contributes to airway remodeling in human by increased proliferation of epithelial cells as well as mucin and growth factors production in asthmatics (Fang *et al.* 2012).

RES (FIZZ-3) is an endogenous agonist of Toll-like receptor 4 (TLR-4) which leads to activation of various genes involved in asthmatic inflammation via NF-κB pathway (Tarkowski *et al.* 2010). Thus, it may be assumed that resistin as the member of RELM-family may play a role in asthma pathogenesis and severity.

There are only a few publication on RES in human asthma with conflicting results reported (Larochelle *et al.* 2007, Kim *et al.* 2008, Arshi *et al.* 2010, Leivo-Korpela *et al.* 2011). Some authors indicate that RES play a role in asthma severity in adults (Larochelle *et al.* 2007, Leivo-Korpela *et al.* 2011). Conversely, studies in children suggest that RES may even reduce risk of asthma (Kim *et al.* 2008) or has no significant influence on disease (Arshi *et al.* 2010).

Thus, the aim of our study is to analyze RES serum levels in children with allergic asthma in relation to BMI and gender. Comparison between serum levels of resistin in children with atopic asthma and healthy controls is also performed.

MATERIAL AND METHODS

The study group was comprised of randomly selected atopic asthma patients from 320 asthmatics who consecutively visited allergy outpatient clinics in Department of Paediatrics in Zabrze, Silesian University of Medicine in Katowice from January 2010 to December 2010. The study was approved by the Ethics Committee of the Medical University of Silesia in Katowice and written informed consent was obtained from children's parents and examined children if over 16 years old.

Finally 89 children (61 boys and 28 girls, aged 7.0-17.0 years; mean age 11.3 ± 0.4 years) with stable atopic asthma were enrolled into study. The diagnosis of asthma, the assessment of its severity, disease management plan and control level were established according to the GINA 2006 criteria (Batemann *et al.* 2008). Twelve children suffered from intermittent, 56 – mild and 32 moderate persistent asthma. Children with severe asthma and asthma exacerbations were excluded from the study. Duration of the disease ranged from 2 years to 6 years. During follow-up visit children underwent spirometric assessment using LUNG TEST 1000 device (Poland) as previously described in details (Ziora *et al.* 2007). All asthmatic children had positive skin prick tests (SPTs) to ≥1 allergens. A positive SPT was defined as a mean diameter of at least 3 mm in the presence of negative diluent and positive histamine controls.

The degree of allergic sensitization was measured by the wheal size of SPTs.

All children had stable, well controlled asthma according to GINA 2006 criteria and no changes were made in chronic anti-inflammatory treatment within the previous 12 weeks. None of the patients reported respiratory tract or other infections at least 3 month prior to the study. Seventy-six children with mild or moderate asthma were treated with regularly inhaled corticosteroids (ICS) at a variable daily dose required to control disease symptoms. At the time of evaluation, daily ICS doses ranged from 100 to 600 μg/day (mean daily dose: 246.7±16.7 μg/day).

The control group consisted of 33 healthy children (20 boys and 13 girls) with normal weight matched for sex and age (aged 7.0–17.0 years; mean age 11.7±3.8 years). Controls had negative history of allergic diseases, negative SPT results to a panel of aeroallergens (dust mite, mixed grass, or tree pollen; cat and dog;

Allergopharma, Reinbek, Germany) and had normal level of total serum immunoglobulin (IgE). These control children without evidence of pulmonary or systemic inflammatory disease attended the outpatient paediatric clinic for non-immunological and non-inflammatory problems and they needed venous blood sample collection.

Anthropometric measurements

Body mass index (BMI) (body weight [kg] divided by height^2) and standard deviation [SD] score for BMI (BMI-SDS) were calculated according to current Polish population predicted values (Palczewska *et al.* 2001). Normal weight was defined as BMI-SDS between –2.0 and +2.0. Obesity was defined as BMI-SDS >2.0.

Laboratory assays

Blood samples for analyses were collected fasting between 07:00 a.m. and 09:30 a.m. Serum resistin concentrations were determined, as previously described (Ziora *et al.* 2011) by ELISA method (*enzyme-linked immunosorbent assay*) using commercially available kit (Bio-Vendor R&D, Czech Republic). Absorbance was measured using spectrophotometer (μQuant, Microplate Reader, Bio-Tek, Winooski, VT, USA) at 450 nm wavelengths. Acquired data were analyzed by KC Junior Software (v.1.31.5, Bio-Tek Instruments, Winooski, VT, USA). The lowest RES concentration determined was 0.01 ng/mL, and the intra- and extra-assay error was 3.4% and 6.8%, respectively.

Statistical analysis

The results were analyzed using a licensed version of Statistica 6.0 software (StatSoft Inc., Tulsa, OK, USA). The distribution of results was tested for consistency with normal using Shapiro-Wilk test. The homogeneity of variance was evaluated using the Levene's test and significance of differences in mean values was assessed by the analysis of variance (ANOVA).

As the Shapiro-Wilk test demonstrated that study variable distributions are significantly different from normal, and the Levene's test indicated the lack of homogeneity of variance, the non-parametric Kruskal-Wallis test and the median test were used in the final assessment. To verify differences between mean values, the HSD (Honestly Significant Difference) Tukey's multiple comparison test was used for different sample sizes. Correlation were tested using the Spearman test.

All results were considered statistically significant at $p<0.05$.

RESULTS

Characteristics of the 89 subjects with asthma and the 33 healthy control subjects is presented in Table 1. Both groups were similar with regard to age and sex. Among studied asthma children 30 (9 girls and 21 boys) were obese (AO) and 59 (19 girls and 40 boys) had normal weigh, normal BMI and BMI-SDS within range of –2 to +2 (ANW). In obese asthmatic children (both girls and boys) BMI and BMI-SDS were significantly higher ($p<0.001$) than in healthy controls. Asthma was well controlled in studied children and the mean values of FEV_1 and FVC in asthmatics did not differ from mean values obtained in control group. Mean values of IgE concentrations in all asthmatic children (both in AO and ANW) were significantly higher than in controls ($p<0.01$).

The mean values of resistin serum levels in all children are shown in Table 2.

The mean serum levels of resistin were significantly ($p<0.01$) higher in all non-obese asthmatic children (4.11±0.1 ng/mL) than in healthy children (3.83±0.1 ng/mL). After stratifying by gender only ANW boys and AO boys had significantly higher RES levels in comparison to boys from control group. Both AO (4.4±0.2 ng/mL) and ANW girls (4.38±0.2 ng/mL) and also girls from control (4.09±0.1) group showed significantly higher mean resistin serum concentrations than boys from corresponding groups (3.99±0.1 ng/mL, 3.83±0.17 ng/mL and 3.44±0.06 ng/mL respectively). concentrations and BMI or BMI-SDS were noticed in asthmatic and healthy children.

We did not find any correlation between RES levels and lung function parameters, allergic sensitization as well as severity of asthma (data not shown).

DISCUSSION

In the present study we provided evidence that in asthmatic children, irrespective to BMI, mean serum RES is different from healthy ones. We observed significantly higher concentrations of plasma resistin in asthmatic children, especially in boys, compared with controls.

Previously, conflicting results on the levels and the role of RES in human asthma have been published. Data from a study by Kim *et al.* (2007) involving 149 atopic asthmatic children, 37 nonatopic asthmatic children, and 54 healthy children suggested the negative predictive role of resistin in asthma. Atopic asthmatic children had lower resistin levels compared with the nonatopic asthmatic and control groups. Resistin plasma levels demonstrated a positive correlation with methacholine PC20 and a negative correlation with eosinophil count and total IgE (Leivo-Korpela *et al.* 2011). In smaller group of 21 children Arshi *et al.* (2010) did not find any difference in serum RES concentrations between children with asthma and healthy.

Our findings rather stay in line with results obtained by Larochelle *et al.* (2008). They documented that plasma resistin levels were significantly higher in adults with moderate to severe persistent asthma than in controls without evidence of pulmonary or systemic inflammatory disease. Resistin levels increased with disease severity, but these elevations in were independent of fasting serum CRP or glucose. Recent study per-

Tab. 1. Demographic characteristic in asthma and healthy children.

	ANW (n=59; 19 girls, 40 boys)	AO (n=30; 9 girls, 21 boys)	H (n=33; 13 girls, 20 boys)
age [years]			
girls	12.4±0.6 (12.0, 4.5)	12.4±2.6 (12.0, 7.5)	13.5±1.2 (14.2, 3.7)
boys	11.8±0.5 (12.5, 5.7)	11.7±1.3 (12.0, 3.0)	11.8±1.6 (11.0, 4.0)
all	12.0±0.8 (12.5, 4.6)	11.9±1.2 (12.7, 6.0)	12.9±1.0 (13.0, 4.0)
BMI [kg/m^2]			
girls	18.2±1.15 (18.9, 4.1)	23.4±2.0 (23.8, 5.1) +	18.8±0.9 (19.1, 3.0)
boy	18.4±0.72 (18.3, 4.1)	25.2±1.8 (25.8, 5.0) ++	17.3±1.1 (16.8, 2.4)
all	18.3±0.61 (18.3, 3.9)	24.6±1.4 (24.8, 4.8) ++	18.3±0.8 (18.0, 3.0)
BMI-SDS			
girls	0.01±0.52 (0.0, 2,3)	3,14±0,54 (3.05, 1.4) ++	-0.19±0.42 (-0.1, 1.3)
boys	0.15±0.27 (0.09, 1.24)	4.49±0.91 (4.18, 3.1) ++	-0.46±0.58 (-0.83, 1.93)
all	0.11±0.25 (0.08, 1.57)	4.09 ±0.69 (3.78, 3.07) ++	-0.29±0.34 (-0.11, 1.87)
FEV1 [% predicted]			
girls	87.3±9.28 (87.0, 32.0)	95.8±6.8 (98.0, 10.0)	98.7±5.8 (102.0, 15.5)
boys	87.2±4.22 (85.0, 19.0)	93.3±8.19 (100.0, 21.0)	90.8±11.9 (87.5, 31.7)
all	87.2±4.1(85.0, 23.0)	94.1±5.9 (99.5, 20.0)	96.06±5.62 (98.0, 19.0)
FVC [% predicted]			
girls	89.29±6.92 (88.0, 15.0)	96.1±5.2 (96.0, 11.0)	97.6±7.7 (99.0, 23.5)
boys	90.5±4.11 (90.1, 16.0)	93.9±6.7 (98.0, 22.0)	93.2±11.4 (95.6, 24.0)
all	89.8±3.5 (88.5, 16.0)	94.6±4.8 (96.5, 15.5)	96.3±6.3 (99.0, 20.0)
IgE [IU/mL]			
girls	485.1±269.3 (284.4, 503.0)	414.4±344.4 (248.8, 292.0)	70.5±39.4 (32.7, 115.7)
boys	355.7±105.8 (272.5, 402.3)	415.2±161.4 (393.7, 396.0)	24.3±16.2 (16.8, 31.7)
all	398.6±111.3 (280.0, 384.5)*	414.9 ±150.7 (329.0, 404.0)*	50.7±25.2 (30.0, 60.7)

Data are shown as: mean±1,96 SE (median, IQR) –i.e. difference between the upper and lower quartiles)
* p<0.01 in comparison to control group
+ p=0.02 in comparison to control group and vs asthmatics with normal weight
++ p<0.001 in comparison to control group and vs asthmatics with normal weight
ANW – asthmatics with normal weight; AO - Asthmatics with obesity; H -healthy controls; IOR – interquartile range; SE – standard error

Tab. 2. Serum resistin concentrations in asthmatic and healthy children.

	ANW (n=59; 19 girls, 40 boys)	AO (n=30; 9 girls, 21 boys)	H (n=33; 13 girls, 20 boys)
resistin (ng/mL)			
girls	4.38±0.2 (4.31, 0.48) ##	4.30±0.15 (4.22, 0.16) #	4.09±0.1 (4.1, 0.3) ##
boys	3.99±0.1 (4.11, 0.39)**	3.83±0.17 (3.97, 0.44)*	3.44±0.06 (3.4, 0.1)
total	4.11±0.1(4.1, 0.37)*	3.98±0.15 (4.1, 0.5)	3.83±0.1 (3.9, 0.7)

Data are shown as: mean±1,96 SE (median, IQR)
ANW – asthmatics with normal weight; AO - Asthmatics with obesity; H -healthy controls; IOR – interquartile range; SE – standard error
* p<0.01, ** p<0.001 in comparison with control group
# p<0.05, ## p<0.01 girls vs boys

formed by AlMutari et al.(2011) revealed that serum resistin concentrations were higher in adult patients with acute asthma compared with these with stable asthma and stable COPD. In the research by Leivo-Korpela *et al.* (2011) performed in non-obese women with newly-diagnosed steroid-naive asthma, high serum RES levels predicted favourable anti-inflammatory effect of inhaled glucocorticoids suggesting that this adipocytokine may be a marker of steroid-sensitive phenotype of asthma. Resistin increased the production of proinflammatory cytokines IL-6 and TNF-α in human macrophages and this effect was inhibited with fluticasone. Serum levels of RES correlated positively with some pulmonary function test (forced vital capacity and vital capacity) (Leivo-Korpela *et al.* 2011).

In our examined children with asthma, serum RES did not correlated with BMI but girls had higher RES levels than boys as it was demonstrated by Gerber *et*

al. (2005). In our previous study (Ziora *et al.* 2011) RES concentrations were related to BMI, but in larger group comprising 4 female subgroups: anorectic, no otherwise specified eating disorders, healthy and obese subjects.

A possible limitation of our study was that it involved children within a wide range of age. Lack of subjects with severe asthma and exacerbation of asthma may also be a drawback of our research. In our study only children with atopic asthma, but not with non-atopic asthma, were investigated. So we cannot state with certainty whether elevated serum RES levels are characteristic for asthma itself or if this finding reflects at least partially atopic status per se. Another limitation of the study was gender bias. Atopic asthma is more prevalent in prepubertal and adolescent boys than in girls, so it was not surprising that in our cohort boys outnumbered girls. However, our study was performed on a specialty clinic sample to minimise the likelihood that children without asthma would be included, and to ensure that consecutive patients who visited allergy outpatient clinics would be enrolled. We did not estimate the BAL-concentration of RES.

We conclude that in atopic childhood asthma, increased resistin serum levels were observed irrespective to obesity. These findings suggest the potential association between RES and atopic asthma especially in girls. However resistin have limited value as potential biomarker in estimation of atopic asthma severity and degree of allergic sensitisation.

Although this was a cross-sectional study with a relatively small sample size, we believe that our data may be a basis for further studies evaluating the possible role of adipokines in childhood atopic asthma pathogenesis.

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