

Serum visfatin levels are decreased in schoolchildren with atopic asthma

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Abstract

OBJECTIVES: Very little is known about the role of adipokines in atopic asthma in children. Studies about the potential role of novel proinflammatory adipocytokine – visfatin are lacking.

DESIGN AND SETTING: In this cross-sectional study serum visfatin (VISF) levels were measured in 89 asthmatic out-patients (61 boys and 28 girls aged 7.0–17.0 years) and in 33 healthy children.

MATERIAL AND METHODS: Among examined asthmatics 59 (19 girls and 40 boys) had normal weight and 30 (9 girls and 21 boys) were obese. Serum VISF was evaluated using standard ELISA tests and the results were analysed in relation to body weight, asthma severity, and gender were analysed.

RESULTS: The mean serum levels of visfatin were significantly ($p < 0.001$) lower both in obese (2.13 ± 0.07 ng/ml) and non-obese asthmatic children (2.05 ± 0.06 ng/ml) than in healthy children (2.57 ± 0.07 ng/ml) regardless of gender. After stratifying by gender, there was a significant decrease ($p < 0.001$) in visfatin levels in obese asthmatic girls (2.30 ± 0.08 ng/ml) and asthmatic girls with normal weight girls (2.21 ± 0.09 ng/ml) compared with girls from control group (2.69 ± 0.06 ng/ml). In obese asthmatic boys and non-obese asthmatic boys also significantly lower ($p < 0.01$) mean values of visfatin (2.03 ± 0.06 ng/ml and 1.9 ± 0.06 ng/ml respectively) were observed than in control boys (2.391 ± 0.09 ng/ml).

No relationships between examined adipokine levels and asthma severity, spirometric parameters, degree of allergic sensitization, BMI, were observed.

CONCLUSION: Visfatin is not potential biomarker in atopic asthma in children and further studies evaluating the possible role of this proinflammatory adipokine in childhood atopic asthma pathogenesis are needed.

Abbreviations:

ALI	- acute lung injury
ANOVA	- analysis of variance
BMI	- body mass index
COPD	- chronic obstructive pulmonary disease
CRP	- C reactive protein
FEV1	- increased forced expiratory volume in 1 second
FVC	- forced vital capacity
GINA	- Global Initiative for Asthma
HSD	- Honestly Significant Difference
ICS	- inhaled corticosteroids
IgE	- immunoglobulin E
IL-1 β	- interleukin 1beta
IL-10	- interleukin 10
IL-1Ra	- interleukin 1 receptor a
IL-6	- interleukin 6
mRNA	- messenger ribonucleic acid
NAD	- nicotinamide
NAMPT	- nicotinamide phosphoribosyltransferase gene
NMN	- nicotinamide mononucleotide
PBEF	- cytokine pre-B colony enhancing factor-1
RA	- rheumatoid arthritis
ROS	- reactive oxygen species
SD	- standard deviation
SDS	- standard deviation score
SPTs	- skin prick tests
TNF- α	- tumor necrosis factor alpha,
VCAM	- 1 vascular cell adhesion molecule
VISF	- visfatin

INTRODUCTION

Obesity is associated with asthma in both adults and children, as shown in cross-sectional, case-control, longitudinal, and weight intervention studies (Beckett *et al.* 2001; Beuther *et al.* 2007; Castro-Rodriguez *et al.* 2001; Figueroa-Muñoz *et al.* 2001; Jartii *et al.* 2009). Some reports demonstrate that the obesity-asthma association is stronger among women and peripubertal girls (Beckett *et al.* 2001). The exact mechanisms for the relationship between obesity and asthma are not known, although mechanical, immunologic, genetic, hormonal, and environmental pathways have been proposed. The immunologic pathway invokes a possible role for pro-inflammatory and anti-inflammatory adipokines produced by adipose tissue as it secretes a large number of pro-inflammatory cytokines and factors modulating immune function.

Although adipose tissue produces over 50 adipokines, the most reports concentrated on the role of pro-inflammatory leptin and anti-inflammatory adiponectin. However, recent data from human studies are inconclusive regarding the independent association between serum leptin or serum adiponectin and the risk of asthma in children and adults (Nagel *et al.* 2009; Sood *et al.* 2006; Sutherland *et al.* 2009). Some findings suggest that leptin and adiponectin might be involved in the causal pathway between obesity and allergic sensitization and asthma in humans (Nagel *et al.* 2009; Sood *et al.* 2006), but other studies do not confirm this hypothesis (Jartii *et al.* 2009).

Another adipokine, resistin, receiving its name from the original observation that it induced insulin resistance in mice (Steppan *et al.* 2001) seems to be involved in asthma pathogenesis and severity in adults (Larochelle *et al.* 2007). Conversely, studies in children suggest that resistin may reduce risk of asthma (Kim *et al.* 2008). Hence, it seems that other adipokines should be additionally explored in relation to asthma risk and asthma severity (Jartii *et al.* 2009).

Visfatin (VISF) is another novel adipokine coded by gene *NAMPT* (nicotinamide phosphoribosyltransferase). VISF mRNA is the most abundantly expressed in the liver and muscles, but also in human heart, brain, placenta, lungs, liver, skeletal muscle, kidney and pancreas (Samal *et al.* 1994). It is also highly expressed and secreted by human visceral adipose tissue hence the term “visfatin” and exerts an insulin-mimetic effect (Fukuhara *et al.* 2005).

It has been demonstrated VISF is identical to the cytokine pre-B colony enhancing factor-1 (PBEF) (Samal *et al.* 1994), and to the extracellular form of nicotinamide phosphoribosyltransferase (Nampt), the rate-limiting enzyme in the NAD salvage synthetic pathway biosynthesis that transforms nicotinamide into nicotinamide mononucleotide (NMN) (Rongvaux *et al.* 2002).

Visfatin dose-dependently upregulates the production of the pro- and anti-inflammatory cytokines interleukin (IL)-1 β , TNF- α , IL-1Ra, IL-6, and IL-10 in human monocytes. Moreover, it increases the surface expression of co-stimulatory molecules CD54, CD40, and CD80 in monocytes (Moschen *et al.* 2007) and inhibits neutrophil apoptosis (Jia *et al.* 2004).

VISF expression and/or serum levels is up-regulated in a variety of acute and chronic inflammatory diseases including sepsis (Jia *et al.* 2004), acute lung injury (Ye *et al.* 2005), rheumatoid arthritis (Otero *et al.* 2006; Brentano *et al.* 2007), inflammatory bowel disease (Tilg & Moschen 2008), psoriasis (Koczan *et al.* 2005) and myocardial infarction and atherosclerosis (Dahl *et al.* 2007), however, the potential association between visfatin and bronchial asthma has not been explored so far.

Thus, the aim of our study was to analyse visfatin plasma levels in children with allergic asthma in relation to body weight and asthma severity. Additionally, we examined the possible differences in serum content of these adipokine with regard to gender.

MATERIAL AND METHODS

The study group was comprised of randomly selected consecutive atopic asthma patients who visited allergy outpatient clinics in the Department of Paediatrics in Zabrze (Medical University of Silesia in Katowice, Poland). The study was approved by the Ethics Committee of the Medical University of Silesia in Katowice (Poland) and written informed consent was obtained from children's parents. Children with asthma exacerbations were excluded from the study.

Finally 89 children (61 boys and 28 girls, mean age 11.34 ± 0.37 years; range 7.0–17.0 years;) with stable atopic asthma were enrolled into the study. The diagnosis of asthma and the assessment of severity and asthma control level were done according to the Global Initiative for Asthma (GINA) 2006 criteria (NIH 2002). Twelve of children had intermittent disease, 56 had mild disease, and 32 had moderate persistent asthma. Children underwent spirometric assessment and presented reversibility of airway obstruction, as documented by a positive response to a bronchodilator of at least 12% increased forced expiratory volume in 1 second (FEV_1). 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. 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 $\mu\text{g}/\text{day}$ (mean daily dose: 246.76 ± 16.70 $\mu\text{g}/\text{day}$). All children with asthma were well controlled according to GINA 2006 criteria (NIH 2002).

The control group consisted of 33 healthy children (20 boys and 13 girls) with normal weight matched for sex and age (mean age 11.71 ± 3.79 years; range 7.0–17.0 years). Controls had negative history of allergic diseases with 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 pediatric clinic for non-immunological and non-inflammatory problems and they needed blood tests to be performed.

Anthropometric measurements

Body mass index (BMI) (body weight [kg] divided by height [m^2]) and standard deviation [SD] score for BMI (BMI-SDS) were calculated according to current Polish populational predicted values (Palaczewska & Niedzwiedzka 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 in the fasting state between 07:00 AM and 09:30 AM. The serum was separated by centrifugation at 1000g for 15 min at $+4^\circ\text{C}$, and immediately stored at -70°C until VISF analysis was performed.

Serum visfatin-C terminal concentrations were measured as previously described (Ziora *et al.* 2012) using commercial human enzyme immunoassay kit according to the manufacturer's protocol (Phoenix Pharma-

ceuticals, Inc, Burlingame, CA, USA). The absorbance measurements for all samples were performed using the Quant Universal Microplate Spectrophotometer (BioTek Instruments Inc, Winooski, VT, USA). The limit of detection was 0,55 ng/ml and the intra-assay and the extra-assay coefficient of variance were ≤ 5 and $\leq 14\%$ respectively.

Statistical analysis

Statistical analysis was performed using Statistica 6.0 software (StatSoft Inc., Tulsa, OK, USA). Normal data distribution was assessed using Shapiro-Wilk test, and the homogeneity of variance was assessed using Levene's test. Comparisons between the examined groups were performed using the ANOVA and post hoc HSD Tukey's multiple comparison test for different sample sizes or Kruskal-Wallis and median tests if data distribution was not normal. Correlations were analyzed by Pearson's linear correlation test or Spearman's test if data distribution was not normal. All results were considered statistically significant at $p < 0.05$.

RESULTS

Characteristics of the 89 subjects with asthma and the 33 healthy control subjects are 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 weight and BMI (ANW).

Children with asthma had significantly ($p < 0.001$) higher IgE levels than healthy controls.

The mean serum levels of visfatin, presented in Table 1, were significantly ($p < 0.001$) lower both in obese (2.13 ± 0.07 ng/ml) and non-obese asthmatic children (2.05 ± 0.06 ng/ml) than in healthy children (2.57 ± 0.07 ng/ml) regardless of gender. After stratifying by gender, there was a significant decrease ($p < 0.001$) in VISF levels in AO girls (2.3 ± 0.08 ng/ml) and ANW girls (2.21 ± 0.09 ng/ml) compared with girls from control group (2.69 ± 0.06 ng/ml). In AO boys and ANW boys also significantly lower ($p < 0.01$) mean values of visfatin (2.03 ± 0.06 ng/ml and 1.9 ± 0.06 ng/ml respectively) were observed than in control boys (2.39 ± 0.09 ng/ml). The mean visfatin levels obtained in girls with asthma and girls from control group were significantly higher than in boys (Table 1).

No significantly relationships between visfatin concentrations and BMI or BMI-SDS were observed in asthmatic and healthy children.

There was no difference in visfatin levels in children with different severity degrees of asthma. In patients with moderate persistent asthma, the mean values of FEV_1 and FEV_1/FVC were significantly lower than in those with intermittent and mild persistent disease ($p < 0.05$). Additionally, serum IgE levels tended to be higher in children with moderate asthma, but this did not reach statistical significance (data not shown). The

severity of asthma was inversely correlated with FEV₁ and FEV₁/FVC ($r=-0.51$, $p=0.001$; $r=-0.36$, $p=0.05$; respectively) and serum IgE levels correlated with a degree of sensitization measured by wheal size of SPTs ($r=0.45$, $p=0.005$).

Tab. 1. Demographic characteristic and visfatin serum concentration 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)
Visfatin (ng/ml) (mean±1.96 SE)			
Girls	2.21±0.09*#	2.35±0.08*#	2.69±0.06#
Boys	1.97±0.06*	2.03±0.06*	2.39±0.09
All	2.05±0.06*	2.13±0.07*	2.57±0.07
Age [years] (mean±1.96 SE)			
Girls	12.4±0.6	12.4±0.4	13.5±0.6
Boys	11.8±0.5	11.7±0.7	11.8±0.8
All	12.0±0.42	11.9±0.6	12.9±0.5
BMI [kg/m²] (mean±1.96 SE)			
Girls	18.2±1.15	23.4±2.0 ⁺	18.8±0.9
Boys	18.4±0.72	25.2±1.8 ⁺	17.3±1.1
Total	18.3±0.61	24.6±1.4 ⁺	18.3±0.8
Weight [kg] (mean±1.96 SE)			
Girls	42.2±2.9	56.5±6.3 ⁺	45.1±2.4
Boys	43.9±2.3	62.2±5.2 ⁺	38.5±3.7
Total	43.4±1.8	60.5±4.1 ⁺	42.5±0.5
Height [cm] (mean±1.96 SE)			
Girls	148.8±3.5	152.8±6.1	153.3±3.0
Boys	151.6±3.1	154.2±4.4	147.1±5.5
Total	150.1±2.4	153.8±3.5	150.8±2.8
FEV1 [% of predicted] (mean±1.96 SE)			
Girls	87.33±9.28	95.78±6.83	98.67±5.80
Boys	87.19±4.22	93.32±8.19	90.83±11.93
Total	87.24±4.11	94.11±5.92	96.06±5.62
FVC [% of predicted] (mean±1.96 SE)			
Girls	89.29±6.92	88.89±5.21	85.90±4.97
Boys	90.50±4.11	81.84±4.93	88.83±5.46
Total	89.81±3.53	84.10±3.89	86.64±4.01
FEV1/FVC [%] (mean±1.96 SE)			
Girls	82.72±4.14	88.89±5.21	85.90±4.97
Boys	79.98±3.28	81.84±4.93	78.83±5.46
Total	80.88±2.59	84.10±3.89	83.54±4.01
IgE [U/l] (mean±1.96 SE)			
Girls	485.1±269.3*	414.4±344.4*	70.5±39.4
Boys	355.7±105.8*	415.2±161.4*	24.3±16.2
Total	398.6±111.3*	414.9±150.7*	50.7±25.2

ANW - asthmatics with normal weight; AO - obese asthmatics; H - healthy subjects; SE standard error

* $p<0.001$ in comparison with control group

⁺ $p<0.001$ in comparison with control group and asthmatics with normal weight

[#] $p<0.01$ girls vs boys

DISCUSSION

In our study we for the first time investigated the potential link between serum visfatin concentrations and atopic asthma condition in schoolchildren.

Surprisingly, opposite to our expectations, among asthmatic children both with normal weight and with obesity we observed decreased mean serum level of visfatin compared with healthy children. No relationship between visfatin level, atopy status and asthma severity was observed. Therefore our findings suggests that in atopic asthma, in contrast to other chronic inflammatory conditions, visfatin cannot serve as a potential biomarker.

Visfatin may be a potential biomarker for example in patients with acute lung injury (ALI). The over-expression of *NAMPT* may adversely affect the pulmonary cell barrier function and contribute to the initiation or aggravation of ALI. Analysis of single nucleotide polymorphisms (SNPs) in the *NAMPT* gene proximal promoter region indicated that a GC haplotype had a nearly 8-fold higher risk of ALI, while a TT haplotype had a lower risk of it (Ye *et al.* 2005). Increased visfatin protein expression was also observed in bronchoalveolar lavage (BAL) fluid and serum in both canine and murine models of lung injury.

Otero *et al.* (2006) reported that patients with rheumatoid arthritis (RA) showed considerably higher plasma levels of visfatin than healthy controls, implicating visfatin as one of the biomarkers in RA. In the study by Brentano *et al.* (2007) increased levels of this adipocytokine in serum and synovial fluid correlated with the degree of inflammation and clinical disease activity in patients with RA.

Results of our study rather stay in line with observations of Eker *et al.* (2010). They reported that among 55 adults with chronic obstructive pulmonary disease (COPD) without malnutrition serum VISF levels were significantly lower than in healthy controls and observed weak but positive correlation between serum visfatin level and forced expiratory volume in the first second (FEV₁). However, Liu *et al.* (2009) noticed significantly higher mean levels of plasma visfatin (2.07 ng/ml) in 35 COPD patients than in 28 healthy controls (1.88 ng/ml). Plasma CRP and TNF- α were positively correlated with visfatin in the COPD group and no significant correlations were found between visfatin and body mass index or percentage of body fat in both groups in this study.

Our asthmatics girls showed significantly higher visfatin levels than boys, but no significant differences were observed between obese and non-obese asthmatics.

It should be emphasized that there are conflicting reports about the relationship between obesity and circulating levels of VISF. Some authors reported increased visfatin plasma levels in obese adult women (Zahorska-Markiewicz *et al.* 2007) or obese children (Araki *et al.* 2008) and demonstrated evident correlations between its plasma concentrations and the

amount of fat (Saddi-Rosa *et al.* 2010). On the other hand, the others observed no apparent relationship between overweight and/or obesity and serum VISF concentrations (Chen *et al.* 2007), or even noted a negative correlation or no relationship of plasma visfatin levels with abdominal circumference (Pagano *et al.* 2006) or visceral fat estimated on the basis of computed tomography (Saddi-Rosa *et al.* 2010). In our previous study (Ziora *et al.* 2012) the mean serum visfatin concentrations in obese girls were significantly higher than in healthy and anorexia nervosa groups.

The potential influence of circulating visfatin on bronchial inflammation and smooth muscle contractility in asthma or COPD is unknown and to our best knowledge there is no such data available up to date. However, there are some evidence that it can directly affect vascular contractility. Visfatin has been shown to induce endothelium-dependent vasorelaxation in rat isolated aorta and mesenteric arteries in the mechanism involving production of nitric oxide (Yamawaki *et al.* 2009). However, recently Valejlo *et al.* (2011) showed that in human mesenteric microvessels VISF may reduce the vasorelaxant responses to different endothelium-dependent vasodilators, such as acetylcholine and bradykinin, without affecting the endothelium independent relaxant capacity of vascular smooth muscle through a mechanism involving NADPH oxidase stimulation and relying on Nampt enzymatic activity (Vallejo *et al.* 2011).

It has been reported that in patients with coronary artery disease visfatin expression is high at plaque rupture sites (Dahl, *et al.* 2007). It accelerates monocyte adhesion to endothelial cells by upregulating intercellular cell adhesion molecule-1 and vascular cell adhesion molecule (VCAM)-1 in vascular endothelial cells due to reactive oxygen species (ROS) overproduction, suggesting a possible role of this adipocytokine in the development of atherosclerosis (Kim *et al.* 2008).

A possible limitation of our study is the wide range of age of involved children. Lack of subjects with severe or exacerbated asthma may be also a disadvantage. We investigated only children with atopic, but not with non-atopic asthma. So that, we cannot state with certainty whether decreased serum visfatin levels are characteristic for asthma itself or rather this finding reflects at least partially atopic status *per se*. However, our study was performed on a particular tertiary clinic sample to minimize the likelihood that the diagnosis of asthma is improper, and to ensure that all consecutive patients who visited allergy outpatient clinic have been enrolled. We did not estimate the BAL-concentration of visfatin.

CONCLUSIONS

In atopic childhood asthma, decreased visfatin serum levels were observed independently of obesity. Although this was a cross-sectional study with a relatively small

sample size, we do believe that our data may be a basis for further studies evaluating the possible role of visfatin in childhood atopic asthma pathogenesis.

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