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Original Article

Differences in adipokines among healthy and asthmatic children

Omar S Al-Attas[1,2], Nasser M Al-Daghri[1,2], Sobhy M Yakout[1,2], Abdullah M Alnaami[1,2], Kaiser Wani[1,2], Majed S Alokail[1,2]

[1]Prince Mutaib Chair for Biomarkers of Osteoporosis, [2]Biomarkers Research Program, Department of Biochemistry, College of Science, King Saud University, Riyadh, Saudi Arabia

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Abstract: Abnormal adipokine levels have been observed to be independent risk factors in the etiology of asthma in certain populations, suggesting possible ethnic differences. The aim of this study was to determine the relationship between adipokines in a cohort of asthmatic Saudi children. 129 Saudi children < 17 years old (58 asthma and 71 healthy) included in the study. Anthropometrics, leptin, adiponectin, resistin and aPAI-1 were measured. Asthmatic subjects had significantly higher systolic blood pressure, glucose, HDL-cholesterol, vitamin D, resistin, and, aPAI-1 than controls ($P < 0.05$). Resistin in particular, remained significantly higher in asthmatic children than controls even after adjusting for age and BMI. In conclusion, among adipocytokines, resistin seems to play an important role in the pro-inflammatory aspect of asthma in children.

Keywords: Adipokines, asthma, resistin, vitamin D, children

Introduction

Asthma is considered as a major cause of morbidity and a main contributor to the high health care expenditure especially in developed countries [1]. The prevalence of asthma have increased during the past 20 years and has emerged as one of the most common non-communicable diseases. It affects 300 million individuals worldwide, responsible for 180 thousand deaths and 15 million DALYs lost each year [2, 3]. In Saudi Arabia, the prevalence of asthma is higher than in other Arab countries, the prevalence of bronchial asthma among Saudi patients is approximately 20-25% [4].

The role of micronutrient deficiencies and genetic polymorphisms in the etiology of asthma and immune regulation has gained considerable attention in recent years [5-7]. Vitamin D is a potent immune system regulator having a potential role in various allergic diseases. A potential role of vitamin D in metabolic syndrome, colorectal cancer, breast cancer, multiple sclerosis, tuberculosis, pneumonia, influenza, respiratory distress [8], depression has been proposed. While various studies have investigated the difference in vitamin D levels between asthmatic and non-asthmatic children [9-13], evidence remains inconclusive [14].

It has been observed that adipocyte regulation is one of the essential non-calcemic activities of vitamin D [15]. 1, 25(OH)2D3 inhibits adipocyte differentiation in the NIH3T3-L1 pre-adipocyte model [16]. Inflammatory functions are linked by a complex cytokine matrix. Asthma is influenced by a different release of lipid mediators, chemokines and cytokines, amongst others. Cytokines play an important role in asthma in triggering allergic inflammatory response, although the exact function of individual cytokine remains to be determined. Cytokines often have overlapping biological activities and exert a multitude of effects at different levels, can excite or inhibit effects of other cytokines and regulate a function via cytokine cascade. Regulating the cytokine network in allergic diseases such as asthma, with expected therapy presents a new but confronting standard for treatment of asthma.

The present study aims to investigate the serum levels of leptin, adiponectin, resistin, and aPAI-

Table 1. General characteristics of subjects

	Children	
	Control	Asthma
N	71	58
M/F	31/40	37/21
	Mean ± SE	Mean ± SE
Age (years)	12.6 ± 0.3	14.2 ± 0.3**
BMI (kg/m^2)	19.7 ± 0.7	22.8 ± 0.9**
Waist (cm)	67.1 ± 1.7	74.6 ± 2.8*
Hips (cm)	77.8 ± 2.1	88.9 ± 2.2**
Systolic BP (mmHg)	102.7 ± 1.2	107.6 ± 1.4*
Diastolic BP (mmHg)	68.7 ± 1.0	69.4 ± 1.2
Glucose (mmol/l)	4.7 ± 0.1	5.4 ± 0.2**
Triglycerides (mmol/l)	1.0 ± 0.05	1.1 ± 0.08
Total Cholesterol (mmol/l)	4.1 ± 0.1	4.2 ± 0.1
HDL-Cholesterol (mmol/l)	1.2 ± 0.04	0.7 ± 0.06**
LDL-Cholesterol (mmol/l)	2.4 ± 0.1	2.1 ± 0.2
Insulin (IU/ml)#	8.7 ± 1.0	14.5 ± 3.3
Leptin (ng/ml)#	19.1 ± 2.8	24.1 ± 4.6
Adiponectin (µg/ml)#	27.5 ± 2.9	20.6 ± 1.6
Resistin (ng/ml)#	21.1 ± 1.4	26.8 ± 1.8**
aPAI-1 (pg/ml)#	26.1 ± 1.4	30.8 ± 2.0*

Note: Data presented as mean ± standard error; significant at P < 0.05; *denotes significance at 0.05 level; **denotes significance at 0.01 level; #denotes non-Gaussian variable.

1 together with 25(OH)D in children with asthma.

Materials and methods

Study subjects

A total of 129 Saudi children < 17 years old were included in the study (58 asthma pediatric patients and 71 healthy controls) were randomly selected from the Riyadh Cohort Study for inclusion. Children and their parents were asked to answer a questionnaire consisting of demographic information. Asthma was based on established questionnaire and doctor diagnosis.

Anthropometrics

Anthropometry included height (rounded off to the nearest 0.5 cm) and weight (rounded off to the nearest 0.1 kg), which were measured using an appropriate international standard scale (Digital Person Scale; ADAM Equipment, Milford, CT, USA), as well as waist and hip circumference in centimeters, which were measured using a standard tape measure. Mean systolic and diastolic blood pressure readings (in mmHg; average of two readings) were taken using appropriate cuffs.

Biochemical parameters

Fasting blood was collected at primary healthcare centers. Blood was drawn, centrifuged and processed on the same day. Both whole blood and serum were placed in plain polystyrene tubes. Serum was delivered to BRP for storage at -20°C. Fasting serum glucose levels, and complete lipid profile (triglycerides, total cholesterol, LDL- and HDL-cholesterol) were determined using routine laboratory methods (Konelab, Espoo, Finland). This biochemical analyzer was calibrated routinely prior to the analysis of all serum samples using quality control samples provided by the manufacturer (Thermo Fisher Scientific, Espoo, Finland).

Serum total 25-hydroxyvitamin D was measured using Roche Diagnostics (e-Cobas 411) in a DEQAS (Vitamin D External Quality Assessment Scheme) accredited laboratory. The inter- and intra-assay coefficients of variation (CV) for 25(OH)D were 5.3% and 4.6%, respectively. Insulin and adipokines (leptin, adiponectin, resistin, and aPAI-1) were quantified using multiplex assay kits (Luminex Corporation, Austin, TX, USA). The intra-assay variation was 1.4%-7.9% and inter-assay variation of < 21% for multiplex parameters assay. Minimum detectable concentration (MDC) was as follows: insulin: 50.9 pg/mL; leptin: 85.4 pg/mL; adiponectin: 145.4 pg/mL; resistin: 6.7 pg/mL and PAI-1, 1.3 pg/ml. Analysis was done in duplicates and protocol was followed. Concentrations were calculated with a 5-parameter model using Luminex IS software ver. 2.3.

Statistical analysis

Data was presented as mean ± standard deviation. Skewed data was either log or Square root transformed. Non Gaussian Variables were represented by Median and Inter quartile ranges. Two samples independent T-test was done to compare control and asthma. Mann Whitney U test was done to compare control and Asthmatic, wherever variables don't follow Gaussian distribution. *P* values < 0.05 were considered as statistically significant. Pearson's correlation test was performed to examine various correlations. Analyses were performed with the

Table 2. Control versus asthma *P*-Values after adjustment for age, BMI and gender

	P-Values
Insulin (IU/ml)#	0.99
Leptin (ng/ml)#	0.33
Adiponectin (μg/ml)#	0.24
Resistin (ng/ml)#	0.009*
aPAI-1 (pg/ml)#	0.54

Note: #denotes non-Normal distribution. *denotes significance at P < 0.05.

Table 3. Vitamin D deficiency (%)

Control		Asthma		All	
Boys	Girls	Boys	Girls	Boys	Girls
36.4	85.7	38.9	55.6	37.9	71.8

Table 4. Associations of 25(OH)D with adipokines

	Children		
	Control	Asthma	All
Insulin (IU/ml)#	-0.120	-0.218	-0.131
Leptin (ng/ml)#	-0.287	-0.198	-0.214*
Adiponectin (μg/ml)#	-0.379*	0.007	-0.246*
Resistin (ng/ml)#	-0.010	-0.120	-0.008
aPAI-1 (pg/ml)#	0.078	0.142	0.113

Note: #denotes non-Normal distribution. *denotes significance at P < 0.05.

SPSS-PC software, version 16.0 (SPSS Inc, Chicago, IL).

Results

The anthropometric, clinical and biochemical of all subjects (58 asthma pediatric patients and 71 healthy controls) are provided in **Table 1**. Data revealed that asthmatic subjects had significantly higher systolic blood pressure (P = 0.03), glucose (P = 0.01), HDL-cholesterol (P = 0.02) vitamin d (P = 0.002), resistin (P = 0.04), and, aPAI-1 (P = 0.01) than controls. In contrast with these results, no significant differences were detected between asthma patients and healthy control subjects in levels of leptin and adiponectin. **Table 1** also shows that mean unadjusted leptin concentrations were higher in participants who had current asthma than in those who had never had asthma.

In **Table 2**, only resistin (P = 0.009) gave significance between control and asthma groups even after adjusting for age, gender, BMI. The rest of the comparisons were not significant.

Table 3 gives the distribution of serum vitamin D deficiency (%) in the asthma and control groups. Serum vitamin D levels of < 50 nmol/l (considered deficient) were found in 37.9% boys and 71.8 girls of all subjects. Vitamin d deficiency was found in 60% of control (36.4 boys and 85.7 girls) compared to 44% deficiency in asthmatic patients (38.9% boys and 55.6% girls).

Linear regression models investigating associations between 25(OH)D serum levels and adipokines in control and asthma groups (**Table 4**). No significance between vitamin d and adipokines in asthma group. There is significant negative correlation between vitamin d and adiponectin and leptin all subjects. An inverse correlation was found between vitamin D and plasma adiponectin in healthy population.

Discussion

In the present study, we have analyzed the association of adipocytokines both in children with and without asthma, establishing possible correlations between such levels and adipocytokines in these subjects. Results showed that children with asthma had HDL cholesterol levels that are significantly lower than non-asthmatic controls. Decreased HDL cholesterol levels are one of the core risk factors of metabolic syndrome even in children [17]. The synthesis of the alveolar surfactant is promoted by HDL particles [18], which suggest that HDL may modulate the progression of inflammation in the lungs. Indeed, several studies have reported that high levels of plasma HDL cholesterol are associated with a decreased risk of allergic diseases [19]. Several studies have found high HDL cholesterol levels to be positively associated with asthma [20], but not all [21]. Our results concur with studies from the Third National Health and Nutrition Examination Survey (NHANES) indicating that elevated serum HDL cholesterol levels associate with better lung function and depressed risk for allergic sensitization in children [22] and adolescents [20].

Data herein show that different levels of adipokines are detected in asthmatic compared to non-asthma control subjects. Adipokines suggested to have an impact on asthma develop-

ment are resistin and aPAI-1. Resistin and aPAI-1 levels were significantly increased in asthmatic individuals compared to non-asthma control subjects. Leptin was increased and adiponectin decreases in asthmatic patients without significance.

Plasminogen activator inhibitor (PAI-1) is a major physiologic inhibitor of the serine proteases, urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA). PAI-1 expression can be regulated by hormones, growth factors, cytokines, and endotoxin in cell cultures [23]. Expression of PAI-1 can either be enhanced or reduced. We found increased levels of PAI-1 in asthmatic subjects. During inflammation, cytokine secretion by neutrophils, monocytes, lymphocytes, and airway epithelial cells is enhanced. This may increase PAI-1 in sputum through different paths. It was previously reported that PAI-1 levels were elevated in the airways of a murine model of chronic asthma and was associated with reduced airway fibrosis in mice [24]. PAI-1 expression was also elevated in the airways of patients with severe asthma [25]. Others showed that elevated levels of plasma PAI-1 are associated with a decline of lung function in subjects with asthma [26]. Furthermore, other studies have also shown that PAI-1 levels in induced sputum samples from subjects with asthma were increased compared with healthy control subjects [27].

In the present study, children with asthma had significantly higher resistin than control subjects. Resistin concentrates around the inflamed tissue, up-grading its own expression and promoting the NFκ-B activation and cytokine production triggering the inflammation [28]. The finding that resistin is increased in subjects with pulmonary inflammation confirms earlier studies [29]. Several studies also observed that resistin is associated with inflammation [30, 31]. Resistin-like molecules (RELM) was initially found in inflammatory zones in a murine model of experimental asthma [32]. It is now believed that the major producer of human resistin reside in macrophages [33] but whether resistin plays a significant role in airway inflammation and even lung remodeling in humans remains a matter of debate. LaRochelle et al showed that steroid-treated patients with moderate-severe asthma had higher levels of resistin than controls, and resistin levels were increased with increasing disease severity [34]. On the contrary, Kim and colleagues found that resistin levels were lower in atopic asthmatic children than in healthy controls, and resistin was associated with lower markers of atopy or bronchial responsiveness [35], while other studies found no difference [36]. The conflicting results are likely explained by differences in patient selection. Asthma is often considered as a single disease entity, but it is actually a syndrome with many different pathological pathways ultimately leading to quite similar clinical presentation: variable airway obstruction with chest tightness, wheezing and cough [37]. The role of adipokines varies extensively between these different inflammatory processes. Furthermore, covariates such as age, sex, fat distribution in the body, menopause, atopy comorbidities and drugs affect these mechanisms and relevance of these factors.

In our study, significantly increasing resistin in asthmatic patients may be explained by an endogenous agonist of Toll-like receptor 4 (TLR4) which leads to gene activation involved in asthmatic inflammation through NF-κB pathway [38]. Accordingly, resistin can enhance the production of pro--inflammatory cytokines IL-6 and TNF-α in human macrophages and interestingly, this effect was inhibited with fluticasone. 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 NFκ-B dependent manner [39].

Despite the reported positive associations between vitamin D status and serum adiponectin as a cause of insulin resistance in individuals [40], in the present study, there is an inverse association of serum adiponectin. This finding is similar to the study by Breslavsky et al [41] and Patel et al [42]. We were also unable to confirm that hypovitaminosis D might induce a higher inflammatory response. In fact, asthma patients with low vitamin D levels did not have lower plasma concentrations of the anti-inflammatory adipokine, adiponectin. The potential effects of vitamin D on adiponectin can be explained by following mechanism. Vitamin D may affect adiponectin through renin-angiotensinogen system. Increased activity of renin-angiotensinogen system is associated with an increased angiotensin production, which leads to the production of altered adipocytes and lower adiponectin production [43]. It should be

noted that two forms of circulating adiponectin are found; low-molecular weight (LMW) and high-molecular weight (HMW) adiponectin. Worthy to note is that both vitamin D and adiponectin are gender sensitive hormones, at least in the Arab population [44], but further stratification was not done due to sample size limitations. Indeed, further studies are recommended with possible interventions that manipulate the gut microbiota which has been shown to alter inflammation and adipokine levels [45].

Despite this limitation, this study includes more advantages. Asthma has often been identified via self-reported surveys as opposed to physician diagnosis. Furthermore, the current study population is unique as it includes patients who are all living in a narrow latitude band in Riyadh area (24.6°N) and all subjects were recruited in the same winter season (Jan-Feb) to be sure that vitamin D levels do not substantially vary on average by season.

In conclusion, altered adipokines levels in asthma patients were observed, resistin in particular. The lack of association between 25(OH)D and adipokines in asthma subjects, does not support a major role of 25(OH)D in the pro-inflammatory environment observed in asthma diseases. Moreover, asthmatic patients with vitamin D deficiency are not characterized by a higher inflammatory state. However, because of this cross-sectional study design, we cannot suggest any causal or temporal relationship. Further investigations are needed to improve our understanding of allergic inflammation and its regulation of adipokines secretion.

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Disclosure of conflict of interest

None.

Address correspondence to: Omar S Al-Attas, Prince Mutaib Chair for Biomarkers of Osteoporosis, Department of Biochemistry, College of Science, King Saud University, Riyadh 11451, Saudi Arabia. Tel: +0096614675939; Fax: +0096614675931; E-mail: omrattas@ksu.edu.sa

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