



Serum Level of Resistin in Asthmatic Children

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Abstract

Objectives: Asthma and intermittent asthma attacks impose a heavy mental and financial burden on families and serum level of resistin influences the incidence of childhood asthma and response to drug therapies. The purpose of this paper was to assess the serum level of resistin in asthmatic children in the division of pulmonary and respiratory diseases at Tabriz Children's hospital.

Materials and Methods: This study was conducted on 50 subjects in the control group and 50 subjects in the case group (asthmatic and healthy prepubertal children under 12 years old with a normal (BMI) (5-84th percentile); asthmatic and healthy overweight prepubertal children under 12 years old (85-94th percentile); and obese prepubertal children under 12 years old (BMI ≥ 95) without any other illnesses. The control group was matched to the case group in terms of age and sex and did not have inflammatory, acute and chronic infectious diseases or a history of medication consumption. Venous blood samples were collected from the subjects after 8 hours of fasting. Serum levels of resistin were measured using Elisa.

Results: The level of resistin increased with asthma severity. Increased weight and BMI also led to a significant increase in the severity of asthma. The serum levels of resistin were significantly higher in the subjects of the control group who did not receive drug therapy. Response to drug therapy was significantly poorer in tall, heavier and high-BMI subjects than in other groups. The number of cases with severe persistent asthma was greater in formula-fed and breastmilk/formula-fed babies. History of allergy or asthma in first-degree relatives was significantly higher in the case group than in the control group ($P=0.001$). Indoor smoking had a significant effect on the type of asthma ($P=0.001$). The history of non-asthmatic allergy had a significant effect on the type of asthma ($P=0.001$).

Conclusions: Obesity and overweight are among the influential factors in the severity of asthma. The amount of resistin is significantly higher in children with severe persistent asthma and uncontrolled asthma than in healthy children. However, the results showed that smoking may also increase serum resistin in at-risk individuals.

Keywords: Asthma, Resistin, Children, Obesity, Environmental factors

Introduction

Epidemiologic studies suggest that the rates of asthma and obesity are rising concurrently (1,2). Moreover, obesity with severe asthma has resulted in unresponsiveness to drug therapy (2,3). The causes of the link between asthma and obesity are not known clearly, but the possible mechanism is said to include a sedentary lifestyle, nutritional factors, genetics, hormonal factors, systemic inflammation and obesity-related declined respiratory capacity, insulin resistance, gastroesophageal reflux, as well as the changes in the immune system by obesity-related factors such as resistin (3,4).

Adipose tissue is an active endocrine organ that generates energy by producing regulatory hormones such as resistin. Macrophage accumulation occurs in obese people and will cause the production of inflammatory cytokines and adiponectin which are associated with not only body mass index (BMI) level but also with obesity-related diseases including cardiovascular atherosclerosis,

type 2 diabetes mellitus, hypertension, and asthma. It was reported in previous studies that resistin is associated with asthma (5, 6). As a 108-amino acid peptide, resistin is part of the cysteine-rich secreted protein family and a possible factor involved in insulin resistance, obesity, and asthma. It has been proposed by various studies as a possible cause of inflammation and allergic responses in atopic asthma (7). Researchers have reported high levels of resistin in patients with atopic asthma (8).

In a study by Muc et al, resistin level was high in overweight asthmatic children and there was a direct relationship between serum level of resistin and severity of asthma (9). In another study on the resistin level in schoolchildren with atopic asthma, increased resistin level was reported in these patients (10). It was reported that patients with asthma have higher levels of resistin and resistin levels increase with the severity of asthma (8).

Considering that asthma and intermittent asthma attacks impose a heavy mental and financial burden on



families and serum level of resistin has been said to affect the incidence of childhood asthma and the response to drug therapies, and since the serum level of resistin is not currently measured in asthmatic children, the purpose of this study was to assess the serum level of resistin in asthmatic children in the division of pulmonary and respiratory diseases at Tabriz Children's hospital.

Materials and Methods

The sample size was calculated to include 44 participants based on Cohen's sample size table for case-control studies with a 95% confidence interval and 0.2 acceptable error. Moreover, 6 more subjects were added to account for non-responding cases. A total of 50 asthmatic and 50 healthy children (all under 12 years old) were assigned to the case and control groups, respectively. The case group included asthmatic prepubertal children with normal BMI (5-84th percentile); asthmatic, prepubertal and overweight children (85-94th percentile); and obese prepubertal children (BMI ≥ 95). The participants in the control group were selected equally from non-asthmatic prepubertal children under 12 years old who had normal BMI (5-84th percentile), were overweight (85-94th percentile) and obese (BMI ≥ 95); these children did not have any diseases and were selected during their visits to the clinic of Tabriz Children's hospital and Sheikh Al-Raeis Clinic for periodical growth monitoring. They were matched to the case group in terms of age and sex and did not have inflammatory, acute and chronic infectious diseases or history of medication consumption. A written consent form was obtained from parents or legal representatives of children and the information forms were filled out through precisely measuring the children's height and weight using measuring station (Seca). Venous blood samples were collected from the subjects after 8 hours of fasting. The serum was separated through low-speed centrifuge, frozen at -70°C in Eppendorf vials, and sent to Danesh Lab for measuring the resistin using the Elisa method. Serum levels of resistin were measured using Elisa kits produced by Mediagnost company, (Reutlingen, Germany). The normal level is 6.48 ng/mL for men and 7.41 ng/mL for women according to the producer's

instructions.

The number of asthma attacks and the severity of asthma were recorded according to The Global Initiative for Asthma (GINA) 2008 guideline. Data collection and blood sampling for resistin measurement were also carried out for the control group. National Center for Health Statistics (NCHS) standard was used as reference for the assessment of growth and nutritional status of children. BMI percentiles were determined for both the case and control groups based on BMI curves, age, and sex.

Simple random sampling was conducted on all of the under 12-year-old asthmatic children who referred to division of pulmonary and respiratory diseases at Tabriz Children's hospital or Sheikh Al-Raeis clinic during 2014. The inclusion criteria were as follows: having complete medical records, being at the prepubertal stage (under 12 years of age), being diagnosed for a minimum of one year, not having any other underlying diseases, not having acute infection over the past two weeks, having BMI >5 th percentile based on age and sex, and not having a history of consumption of other medications (except anti-asthmatics) and oral glucocorticoids over the last 6 months. Children who did not meet one of the above-mentioned criteria or those whose parents or legal representatives did not consent to their participation were excluded.

Results

The findings of this study showed that serum level of resistin was influenced by the type of asthma according to GINA 2008 (Table 1), and it rose with increased asthma severity. Moreover, asthma was more severe in tall subjects, but not significantly different from the control group. Increased weight and BMI also led to a significant rise in the severity of asthma. Other parameters did not show any significant relationship.

Serum levels of resistin varied significantly depending on the grouping of response to drug therapy, and the responses to drug therapy declined significantly as resistin increased. The response to drug therapy was significantly poorer in tall subjects than in other groups. Increased weight and BMI also led to a significant decrease in the

Table 1. Type of Asthma According to GINA 2008 Guideline

	Resistin	Asthma Onset Age	Height	Weight	BMI	Birth Weight	Maternal Delivery Weight	Age
Intermittent asthma	9.06 \pm 0.18 ^a	7.54 \pm 0.52	137.72 \pm 3.72 ^a	33.63 \pm 2.93 ^a	17.30 \pm 0.61	3.42 \pm 0.05	24.45 \pm 1.39	9.59 \pm 0.65
Mild persistent asthma	12.17 \pm 0.40 ^a	7.46 \pm 0.38	138.84 \pm 2.46	35.15 \pm 2.11 ^a	18.03 \pm 0.48	2.91 \pm 0.27	23.76 \pm 1.40	9.46 \pm 0.42
Moderate persistent asthma	18.14 \pm 0.12 ^{a,b}	7.33 \pm 0.55	142.91 \pm 2.54	40.70 \pm 1.85 ^b	19.78 \pm 0.32	3.38 \pm 0.08	24.50 \pm 1.22	9.25 \pm 0.70
Severe persistent asthma	35.93 \pm 0.80 ^{a,b}	6.70 \pm 0.42	153.13 \pm 2.02 ^{a,b}	53.06 \pm 2.20 ^{a,b}	22.44 \pm 0.35 ^{a,b}	3.39 \pm 0.07	23.86 \pm 1.12	8.36 \pm 0.49
Control group	4.07 \pm 0.24	6.87 \pm 0.37	143.86 \pm 1.58	40.07 \pm 1.80	18.89 \pm 0.52	3.17 \pm 0.07	23.83 \pm 0.53	9.12 \pm 0.29
Significance	0.001	0.653	0.001	0.001	0.001	0.063	0.980	0.556

^a show a significant difference with Control group.

^b show a significant difference with Intermittent asthma.

Table 2. Response to Drug Therapy

	Resistin	Asthma Onset Age	Height	Weight	BMI	Birth Weight	Maternal Delivery Weight	Age
Controlled	9.43±0.39 ^a	8.00±0.50	140.18±3.55	35.45±2.90	17.64±0.63	3.24±0.18	24.27±1.44	10.09±0.6
Slightly controlled	15.12±0.66 ^{ab}	7.29±0.32	140.41±1.81	37.56±1.53	18.84±0.35	3.21±0.14	24.33±0.93	9.25±0.39
Uncontrolled	35.93±0.80 ^{ab}	6.70±0.42	153.13±2.02 ^{ab}	53.06±2.20 ^{ab}	22.44±0.35 ^{ab}	3.39±0.07	23.86±1.12	8.36±0.49
Control group	4.07±0.24	6.85±0.37	143.86±1.58	40.07±1.80	18.89±0.52	3.17±0.07	23.83±0.53	9.12±0.29
Significance	0.001	0.220	0.002	0.001	0.001	0.609	0.962	0.198

^a show a significant difference with Control group.

^b show a significant difference with Intermittent asthma.

response to drug therapy. Other parameters did not show any significant difference (Table 2).

There was no statistically significant difference between the case and control groups in sex ($P=0.579$). There was also no statistically significant difference between male and female subjects in the type of asthma based on GINA 2008 guideline ($P=0.978$). No statistically significant difference was found between male and female subjects in the response to drug therapy ($P=0.911$).

Assessment of nutritional status over the first six months after birth showed no significant difference between the case and control groups ($P=0.535$), but it showed a statistically significant difference among the five groups in terms of the type of asthma ($P=0.010$) and the number of cases with severe persistent asthma was higher in formula-fed and breastmilk/formula-fed children. The assessment also revealed a statistically significant difference between the four groups in terms of the response to drug therapy ($P=0.018$) and the rate of uncontrolled asthma was higher in formula-fed and breastmilk/formula-fed children.

No significant difference was found between the case and control groups in the residential area ($P=1.000$). No significant association was also found between the residential area and the type of asthma ($P=0.895$) and between the residential area and the response to drug therapy ($P=0.995$).

The history of allergy or asthma in first-degree relatives was significantly more prevalent in the case group than in the control group ($P=0.001$). It was also significantly more prevalent in “severe persistent asthma” and “moderate persistent asthma” groups than in other groups ($P=0.001$). The history of allergy and asthma in first-degree relatives was significantly more prevalent in the “uncontrolled and slightly controlled” groups than in other groups ($P=0.001$).

No significant difference was found between the case and control group in terms of parental relatedness ($P=0.219$). Parental relatedness did not have a significant effect on the type of asthma ($P=0.101$). It did not have a significant effect on the response to drug therapy either ($P=0.144$).

Indoor smoking was significantly different across the case and control groups ($P=0.001$). It had a significant effect on the type of asthma ($P=0.001$) and was more

prevalent in cases with severe and moderate persistent asthma. Indoor smoking also had a significant effect on the response to drug therapy ($P=0.001$) and was more prevalent in cases with slightly controlled and uncontrolled asthma.

The case and control groups did not have a statistically significant difference in the history of non-asthmatic allergy ($P=0.065$). The history of non-asthmatic allergy had a significant effect on the type of asthma ($P=0.001$) and the history of allergy was more prevalent in the cases with severe persistent asthma. The history of non-asthmatic allergy also had a significant effect on the response to drug therapy ($P=0.001$) and it was more prevalent in the cases with uncontrolled asthma.

Regarding the history of medication consumption (except anti-asthmatics) over the last 6 months, there was no significant difference between the case and control groups ($P=0.886$). It did not have a significant effect on the type of asthma ($P=0.295$) and on the response to drug therapy ($P=0.164$); the history of non-asthmatic allergy was more prevalent in uncontrolled cases of asthma.

No significant difference was observed across the groups in terms of the history of non-asthmatic acute and chronic inflammation and acute infectious disease over the last 6 months.

Discussion

The results showed that the serum level of resistin was influenced by the type of asthma according to GINA 2008 and that it would rise with increased severity of asthma. It was also very high in the serum of the patients with uncontrolled asthma.

The results of a study on children in Arab countries showed that the level of resistin was 24.1 ng/mL in the case group and 17.6 ng/mL in the control group, showing a significant difference between the two groups.

A study showed that weight loss improved systemic inflammation markers in obese children with bronchial asthma in Saudi Arabia (11). In another study, 9 obese children performed aerobic exercises over eight weeks, but the levels of resistin, adiponectin, leptin, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α) and CRP did not show a significant change, which suggests that in the absence of weight loss, the exercise alone does not

affect hormones (12). Moreover, the results of a study suggested that weight gain in asthmatic children increased visits to emergency rooms and mobile units in addition to the consumption of oral and inhaled corticosteroids (12). Some studies suggest that children with moderate and severe obesity respectively are 37 and 68% more likely to develop asthma (14, 15); however, some researchers have not reported any relationship (16).

A study on 60 asthmatic and 20 healthy children showed that the levels of resistin and leptin were significantly higher in the asthmatic than the healthy children. This difference was even higher in cases with severe asthma (17).

The results of another research showed that the level of resistin was significantly higher in asthmatic adults than in healthy individuals and that its rise was accompanied by increased clinical complications (8). Researchers believe that resistin plays a role in systematic inflammation in asthmatic children (17). It raises the production of pro-inflammatory cytokines IL-6 and TNF- α in human macrophages. In addition, resistin expression will increase inflammatory factors such as IL-1, IL-6, TNF- α , and LPS (18, 19). Therefore, high levels of resistin may reflect an asthmatic phenotype characterized by the increased activity of NF- κ B (20). The results of the present study also showed that resistin levels were significantly higher in asthmatic than in healthy children, which is in line with previous findings.

One study showed that the levels of resistin and insulin were significantly higher in patients with chronic obstructive pulmonary disease, acute asthma, and persistent asthma than in healthy individuals. Moreover, resistin levels were significantly different among patients with chronic asthma and acute asthma (2). Similar to asthmatic individuals, smokers had high levels of resistin (2). The present study showed that asthma and resistin levels were significantly higher among the children who had been exposed to smoking; these findings are consistent with previous studies.

The serum level of resistin was 35 ng/mL in the asthmatic obese children, 20 ng/mL in the asthmatic non-obese children, and 10 ng/mL in the control group. However, the resistin level was reduced in the asthmatic children following eight weeks of inhaled corticosteroid consumption (21). Another study showed that the levels of resistin, IgE, IL-4, and IgG-4 were significantly higher in asthmatic children than in non-asthmatic children (22). The findings of the present study also showed that weight and BMI were higher in children with severe persistent asthma and controlled asthma; this confirms previous results about the relationship between obesity and asthma.

Resistin is a protein mediator secreted by adipocytes and macrophages in the adipose tissue (23). It is part of the cysteine-rich protein family (24) also known as resistin-like molecules. Resistin in humans is found the most in several tissues including bone marrow, lungs

(25), placental tissue (26), and pancreatic islet cells (27), respectively. It is responsible for the complications caused by the effect of obesity on glucose and lipid metabolism. In particular, hypoxia in the adipose tissue of obese patients will lead to the uncontrolled production of adiponectin and affect the resistin level (28,29).

Conclusions

The present study showed that obesity and overweight are among the influential factors in the severity of asthma. It also suggested that resistin levels are significantly higher in children with severe persistent asthma and uncontrolled asthma than in healthy children. Moreover, the results displayed that smoking can increase the serum level of resistin in at-risk children.

Conflict of Interests

Authors have no conflict of interests.

Ethical Issues

This study was approved by the ethical committee of Tabriz University of Medical Sciences.

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