Clinical Phenotype “Obesity-Asthma” as One of the Main Problems of Personalized Pulmonology

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Abstract

Background: Asthma is a heterogeneous disease comprising different phenotypes. One of the most common asthma phenotypes is the obesity-asthma phenotype, since obesity affects over a third of the world's population today. It is important to continue investigating possible underlying mechanisms of the interaction between asthma and obesity. **The purpose** of this study was to evaluate levels of leptin, adiponectin, neuropeptide Y (NPY), total oxidative damage (TOD), and total antioxidant status (TAS) in patients with asthma and different body weight (BW), and to analyze their association with spirometry parameters.

Materials and Methods: The study included 27 men and 86 women diagnosed with moderate asthma (mean age of 57.81 ± 13.05 years). During the study, all asthma patients were divided into 3 groups. Group 1 included 37 patients with normal BW, Group 2 included 38 overweight patients, and Group 3 included 38 patients with obesity. We analyzed complaints, anamnesis data, objective status data, and laboratory (blood levels of NPY, adiponectin, leptin, total antioxidant status, and total oxidative damage) and instrumental data (spirometry). Two questionnaires were used: Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Test (ACT).

Results: The leptin level was significantly higher in Group 3 compared to Groups 1 and 2 ($P=0.000$). The NPY level was significantly lower in Group 1 compared to Groups 2 and 3 ($P=0.000$). The TAS value was significantly higher in Group 1 compared to Groups 2 and 3 ($P=0.000$) and the TOD value in Group 1 was significantly lower than in Group 3 ($P=0.038$). The leptin level positively correlated with BMI and waist circumference, and had an inverse correlation with FEV_1 and vital capacity (VC). The adiponectin level had a positive correlation with the Tiffno index, FEF_{50} , and peak expiratory flow (PEF). The NPY level had an inverse correlation with VC, FEV_1 , FEF_{25} , FVC, Tiffno index, FEF_{50} , and PEF.

Conclusion: The severity of the clinical course of moderate asthma in obese patients is associated with different factors, including oxidative stress and levels of leptin, adiponectin and NPY. (*International Journal of Biomedicine*. 2019;9(2):117-120.)

Key Words: asthma • body weight • oxidative stress • leptin • adiponectin • neuropeptide Y

Abbreviations

BMI, body mass index; **BW**, body weight; **FEV_1** , forced expiratory volume in 1 sec; **FEF**, forced expiratory flow; **FVC**, forced vital capacity; **NPY**, neuropeptide Y; **OS**, oxidative stress; **PEF**, peak expiratory flow; **TAS**, total antioxidant status; **TOD**, total oxidative damage; **VC**, vital capacity; **WC**, waist circumference.

Introduction

According to the Global Initiative for Asthma (GINA), asthma is a serious disease, which affects around 300 million people worldwide. One of the most important factors for

clinicians is that asthma is a heterogeneous disease. It is the heterogeneity of the disease that dictates the need for the most individualized treatment.^(1,2) The heterogeneity of both clinical manifestations of asthma and response to therapy is considered nowadays.^(3,4) We distinguish many asthma phenotypes, and even subphenotypes, based on those factors.⁽⁵⁻⁷⁾ Currently, the search for special pathological and molecular features of asthma phenotypes continues, which can become the basis for the development of individual therapy. One of

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the most common asthma phenotypes is the obesity-asthma phenotype, since obesity affects over a third of the world's population today. It is also estimated that the prevalence of obesity will continue to grow and by 2030, about 38% of the world's adult population will be overweight and 20% will be obese.⁽⁸⁾ Considering all of the above, it is important to continue investigating possible underlying mechanisms of the interaction between asthma and obesity. Adiponectin, leptin, OS, and NPY remain relevant in this field of study.

The purpose of this study was to evaluate levels of leptin, adiponectin, NPY, TOD, and TAS in patients with asthma and different BW, and to analyze their association with spirometry parameters.

Materials and Methods

The study included 27 men and 86 women diagnosed with moderate asthma aged from 18 to 75 years (mean age of 57.81 ± 13.05 years).

The study was approved by the Ethics Committee of Voronezh State Medical University named after N.N. Burdenko. (Protocol № 1 from February 21, 2018). Written informed consent was obtained from each patient.

Exclusion criteria were patients' refusal to participate in this study; asthma exacerbation; acute and chronic neurological, psychiatric and endocrinological disorders at the time of examination; chronic diseases in the acute stage; severe and decompensated diseases of liver and kidneys; severe and decompensated cardiovascular diseases (acute period of myocardial infarction, unstable angina, transient ischemic attack, intracerebral hemorrhage, acute heart failure, etc.); cancer; multiple organ failure of different genesis; cancer; pregnancy and lactation; severe infectious diseases.

The asthma diagnosis was based on the integral assessment of symptoms, medical history, health status, and spirometry values according to the Global Strategy for Asthma Management and Prevention.⁽⁹⁾

We analyzed complaints, anamnesis data, objective status data, and laboratory and instrumental data (spirometry with a 400-mg salbutamol test), and we measured levels of NPY, adiponectin, leptin, total antioxidant status, and total oxidative damage.

The levels of leptin and adiponectin were measured using the appropriate reagent kits for quantitative determination of leptin and adiponectin in serum. The determination of TOD was carried out with use of a reagent kit to determine the degree of TOD to biological molecules (PerOx (TOS) (Oxidative Capacity)). We determined the overall antioxidant status by using reagents for determining TAS (ImAnOx (TAS) (Antioxidative Capacity)). NPY levels were measured with a reagent kit for NPY determination in serum.

Two questionnaires were used in this study: Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Test (ACT). All patients received standard asthma therapy.

All data was evaluated with STATGRAPHICS Plus 5.1. Baseline characteristics were summarized as frequencies and percentages for categorical variables and as mean $\pm$ SD for continuous variables. Student's unpaired t-test was used

to compare two groups for data with normal distribution. Group comparisons with respect to categorical variables are performed using the Chi-square test. Multiple comparisons were performed with one-way ANOVA and Tukey's HSD Post-hoc Test. Pearson's correlation coefficient (r) was used to determine the strength of the relationship between the two continuous variables. A probability value of $P < 0.05$ was considered statistically significant.

Results

During the study, all asthma patients were divided into 3 groups. Group 1 included 37 patients with normal BW, Group 2 included 38 overweight patients, and Group 3 included 38 patients with obesity. The three groups did not differ with regard to age and sex (Table 1).

Table 1.

General characteristics of patients

Parameters	Group 1 (n=37)	Group 2 (n=38)	Group 3 (n=38)
Women, n (%)	12 (32.4)	8 (21.1)	7 (18.4)
Men, n (%)	25 (67.6)	30 (78.9)	31 (81.6)
	$P > 0.05$		
Age, years	54.43 ± 16.93	58.68 ± 9.94	60.21 ± 10.96
	$F = 0.0535; P = 0.9480$		
Higher education, n (%)	25 (67.6)	16 (42.1)	9 (23.7)
Specialized secondary education, n (%)	8 (21.6)	14 (36.8)	22 (57.9)
Secondary education, n (%)	4 (10.8)	8 (21.1)	7 (18.4)
	$\chi^2 = 15.875; P = 0.003$		
Married, n (%)	13 (35.1)	6 (15.8)	22 (57.9)
Single, n (%)	24 (64.9)	32 (84.2)	16 (42.1)
	$\chi^2 = 14.602; P = 0.0007$		

Laboratory test results are presented in Table 2. The leptin level was significantly higher in Group 3 compared to Groups 1 and 2 ($P = 0.0000$). No statistically significant differences in adiponectin levels were found in the studied groups. The NPY level was significantly lower in Group 1 compared to Groups 2 and 3 ($P = 0.0000$). The TAS value was significantly higher in Group 1 compared to Groups 2 and 3 ($P = 0.0000$). The value of total oxidative damage in Group 1 was significantly lower than in Group 3 ($P = 0.0382$).

Correlation coefficients between laboratory and spirometry data are presented in Table 3. The leptin level positively correlated with BMI ($r = 0.56; P < 0.05$) and WC ($r = 0.42; P < 0.05$), and had an inverse correlation with FEV₁ ($r = -0.28; P < 0.05$) and VC ($r = -0.29; P < 0.05$). The adiponectin level had a positive correlation with the Tiffno index ($r = 0.51; P < 0.05$), FEV₅₀ ($r = 0.37; P < 0.05$), and PEF ($r = 0.33; P < 0.05$). The NPY level had an inverse correlation with VC ($r = -0.75; P < 0.05$), FEV₁ ($r = -0.57; P < 0.05$), FEV₂₅ ($r = -0.53; P < 0.05$), FVC ($r = -0.45; P < 0.05$), Tiffno index ($r = -0.32; P < 0.05$), FEV₅₀ ($r = -0.41; P < 0.05$), and PEF ($r = -0.38; P < 0.05$).

Table 2.

Laboratory test results in the studied groups

Parameters	Group 1	Group 2	Group 3	Statistics
Leptin, ng/ml	13.01±1.97	11.32±1.99	22.36±1.97	F=343.0272 P=0.0000 P ₁₋₂ =0.0010 P ₁₋₃ =0.0000 P ₂₋₃ =0.0000
NPY, ng/ml	0.31±0.02	0.48±0.02	1.19±0.25	F=386.0549 P=0.0000 P ₁₋₂ =0.0000 P ₁₋₃ =0.0000 P ₂₋₃ =0.0000
TAS, µmol/l	535.78±64.35	277.59±63.49	287.96±63.49	F=196.0883 P=0.0000 P ₁₋₂ =0.0000 P ₁₋₃ =0.0000 P ₂₋₃ =0.7588
TOD, µmol/l	877.70±623.33	1177.75±1022.51	1454.69±1257.72	F=3.0876 P=0.0496 P ₁₋₂ =0.4026 P ₁₋₃ =0.0382 P ₂₋₃ =0.4553
Adiponectin, µg/ml	23.66±11.03	23.40±11.29	23.70±10.25	F=0.0085 P=0.9915

Table 3.

Correlation coefficients between laboratory and spirometry data

Parameters	FEV1	FVC	VC	Tiffno	FEF 25%	FEF 50%	FEF 75%	PEF	BMI	WC
Adiponectin	0.04	-0.08	-0.07	0.51*	0.05	0.37*	0.24*	0.33*	-0.06	0.12
Leptin	-0.28*	-0.25	-0.29*	-0.18	-0.11	-0.23	-0.15*	-0.15*	0.56*	0.42*
NPY	-0.57*	-0.45*	-0.75*	-0.32*	-0.53*	-0.41*	-0.18	-0.38*	0.20	0.05
TAS	-0.03	0.43*	0.36*	-0.40*	0.00	-0.33	-0.42*	-0.36*	-0.32*	-0.15
TOD	0.23	0.22	0.07	-0.43*	0.18	-0.08	0.04	-0.01	0.50*	0.48*

* -P-value <0.05.

Discussion

Our study showed that levels of leptin, NPY and TOD were significantly higher and the TAS level was significantly lower in asthmatic patients with obesity compared with asthmatic patients who were overweight or had normal body weight, indicating inflammatory activity. According to GINA (2019), obesity is a state of chronic low-grade inflammation with increased adipocyte-driven proinflammatory activity. Adipose tissue cells secrete adipokines, and the role of such adipokines as leptin and adiponectin in asthma continues to be investigated. Studies show that there is a correlation between BW and levels of leptin, even though there is also a gender difference: women with the same BMI as men have higher concentrations of leptin.⁽¹⁰⁾ Leptin is a proinflammatory cytokine and might be one of the contributing factors to the higher prevalence of asthma in obese patients. It stimulates release of NO, IL-6 and IL-8 and TNF- α .⁽⁶⁾ At the same time, an experimental study on mice found that administration of TNF- α led to an increase of leptin levels.⁽¹¹⁾ Higher levels of leptin are associated with asthma; this association is stronger in women than men, and more pronounced in premenopausal women than in postmenopausal women.⁽¹¹⁾

On the other hand, adiponectin plays an opposite role, inhibiting inflammation. Our study also showed that

adiponectin functions as an inhibitor of inflammation in asthma, since it had a positive correlation with spirometry parameters. The data about the association between asthma and adiponectin are contradictory. Some studies suggested that low levels of adiponectin are associated with greater odds for asthma in women,^(12,13) while others deny any correlation at all.^(14,15) Other studies report that higher levels of adiponectin correlate with milder asthma, but only in women, while in men this association is the opposite: asthma that required more frequent use of medication was associated with higher adiponectin levels.^(16,17) There was also a study that analyzed serum adiponectin levels and expression of adiponectin mRNA in abdominal adipose tissue in obese patients. Patients with obesity and asthma had lower adiponectin mRNA expression than obese patients without asthma, but levels of serum adiponectin did not differ significantly in these groups.⁽¹⁸⁾ There is also information about decreased levels of serum adiponectin, but only during exacerbations in asthma patients.⁽¹⁹⁾ These data invoke a thought that a decreased level of adiponectin might be not the predictor, but the consequence of asthma's clinical course.

OS plays an important role in asthma. According to the latest research, biomarkers of OS are higher in patients with obesity and correlate with BMI,⁽²⁰⁾ and at the same time antioxidant defense biomarkers have an inverse correlation

with BW.⁽²¹⁾ In our study, we observed the same association in asthmatic patients with different BW.

There are limited studies on the association between NPY and asthma. A few studies report that certain genotypes of NPY are associated with asthma.^(22,23) Y1 receptors of NPY play an important role in allergic inflammation of respiratory airways.⁽²⁴⁾ One study also reports that during asthma exacerbations, levels of NPY increase.⁽²⁵⁾ In our study, levels of NPY were significantly higher in obese and overweight asthmatics and had an inverse correlation with spirometry parameters, indicating a negative effect on the clinical course of asthma.

In conclusion, it can be said, that the severity of the clinical course of asthma in obese patients is associated with different factors, including OS and levels of leptin, adiponectin and NPY. Exact mechanisms remain unclear. Also in this study, we included only patients with moderate asthma, did not analyze gender differences, and did not differentiate between women of premenopausal and postmenopausal age. Further research is required.

Competing Interests

The authors declare that they have no competing interests.

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