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STUDIES OF ASTHMA CONTROL IN PATIENTS WITH METABOLIC SYNDROME

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ABSTRACT

Every day, a practitioner is faced with the problem of patient comorbidity. Bronchial asthma is a common problem, as is metabolic syndrome. Due to the increase in allergic diseases and lifestyle changes, patients may have a combination of metabolic syndrome and bronchial asthma. This combination has been shown to aggravate the course of asthma. Therefore, we wanted to confirm or refute this with our study. The study design included 94 patients with a diagnosis of asthma. A comparative analysis of the spirographic study data revealed that patients with asthma + MetS had statistically significant differences ($p<0.05$). The analysis of anthropometric data revealed that patients with the highest BMI and body weight had a significantly more severe course of asthma ($p<0,05$), which is consistent with the data of available world studies [24, 25], and a positive correlation was found between BMI, percentage of body fat and lower percentage of body fat in patients with severe asthma ($\rho=0,89$, $\rho=0,90$, $\rho=0,87$; $r=0,88$, $r=0,91$, $r=0,90$, respectively). The data obtained indicate the need for individual management of patients with comorbidities, including MetS and asthma, to prevent severe asthma, which is associated with inadequate asthma control and poor quality of life.

KEYWORDS

Bronchial Asthma, Metabolic Syndrome, Body Mass Index, Obesity, Comorbidity

CITATION

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Introduction.

The first mention of ‘syndrome X’ by G. M. Riven in the late 1980s revolutionized the way we think about this issue and marked the beginning of a new perspective and management of what we now call ‘metabolic syndrome’ or ‘insulin resistance syndrome’ [1]. Today, asthma and the metabolic syndrome (MetS) are common social diseases and serious public health problems. Studies have identified a variety of external and internal factors that influence the development and manifestation of asthma, with obesity becoming a key risk factor for MetS.

Metabolic syndrome is a set of related risk factors of metabolic origin that can lead to a variety of systemic diseases in humans.

Literature survey.

The metabolic syndrome is defined by a combination of physiological, biochemical, clinical and metabolic factors that directly increase the risk of atherosclerosis, type 2 diabetes (T2DM) and all-cause mortality [2]. Due to the different definitions and attempts to reach a consensus, the joint working group made a statement that the proposed criteria for adult MetS should include 3 of the following 5 criteria [3, 4, 5].

At present, there are certain features of the definition of MetS, which are shown in Table 1.

Table 1

Definition of metabolic syndrome in adult [6]

Parameters	**NCEP ATP3 2005**	**IDF 2009**	**EGIR 1999**	**WHO 1999**	**AACE 2003**
		Insulin resistance or fasting hyperinsulinemia (i.e. in the upper 25% of the laboratory reference range)	Insulin resistance in the upper 25%; fasting glucose ≥6.1 mmol/l; 2-hour glucose ≥7.8 mmol/l	Insulin resistance in the upper 25%; fasting glucose ≥6.1 mmol/l; 2-hour glucose ≥7.8 mmol/l	High risk of insulin resistance or BMI ≥25 kg/m2 or waist circumference ≥102 cm (men) or ≥88 cm (women)
Number of anomalies	**≥3 з:**	**≥3 з:**	**I ≥2 з:**	**I ≥2 з:**	**I ≥2 з:**
Glucose	Fasting blood glucose ≥5.6 mmol/l or medication for high blood glucose	Fasting glucose ≥5.6 mmol/l or diagnosed diabetes	Fasting glucose level 6.1-6.9 mmol/l		Fasting glucose ≥6.1 mmol/l; Glucose level ≥2 hours 7.8 mmol/l
HDL cholesterol	<1.0 mmol/l (men); <1.3 mmol/l (women) or medication for low HDL cholesterol	<1.0 mmol/l (men); <1.3 mmol/l (women) or medication for low HDL cholesterol	<1.0 mmol/l	<0.9 mmol/l (men); <1.0 mmol/l (women)	<1.0 mmol/l (men); <1.3 mmol/l (women)
Triglycerides	≥1.7 mmol/l or medication for high triglyceride levels	≥1.7 mmol/l or medication treatment of high triglycerides	or ≥2.0 mmol/l or drug treatment of dyslipidemia	or ≥1.7 mmol/l	≥1.7 mmol/l
Obesity	Waist ≥102 cm (men) or ≥88 cm (women)	Waist ≥94 cm (men) or ≥80 cm (women)	Waist ≥94 cm (men) or ≥80 cm (women)	Waist/hip ratio >0.9 (men) or >0.85 (women) or BMI ≥30 kg/m^2	
Hypertensive disease	≥130/85 mmHg or medical treatment of hypertension	≥130/85 mmHg or medical treatment of hypertension	≥140/90 mmHg or medication for hypertension	≥140/90 mmHg	≥130/85 mmHg

Notes: NCEP - Third Report of the National Cholesterol Education Program Expert Panel, IDF - International Diabetes Federation, EGIR - Insulin Resistance Investigation Group, WHO - World Health Organization, AACE - American Association of Clinical Endocrinologists, HDL - high-density lipoprotein cholesterol.

It has been established that obese patients have a high risk of developing asthma. In addition, patients with a combined course of asthma and obesity have a more pronounced symptom complex, reduced response to certain therapies and a greater number of exacerbations of asthma attacks, which generally leads to a decrease in quality of life [7]. The concepts that are used to understand the pathophysiology of many pulmonary disorders are changing, and as a result, progress is being made in understanding the metabolic mechanisms of disease.

The state of systemic inflammation caused by the metabolic syndrome can be a predictor of asthma development and, as mentioned above, can affect the severity of asthma, asthma management and quality of life [8, 9]. The combined course of MetS and asthma is not sufficiently covered in the available publications, so we wanted to study it in more detail in our study.

It has been established that asthma is a diverse disease that can be caused by various underlying pathological processes. 'Asthma phenotypes' are identified groups of randomized demographics, clinical and/or pathophysiological features [10, 11, 12]. There are a number of different clinical manifestations of asthma. Some of the common manifestations include allergic asthma, non-allergic asthma, adult asthma (late onset), asthma with permanent airflow limitation and asthma in the setting of obesity. Sometimes obese asthma patients have severe asthma symptoms but only mild eosinophilic inflammation. In addition to elevated triglyceride levels and lower HDL cholesterol, as shown in Table 1, the metabolic syndrome also includes elevated blood pressure and T2DM. However, the underlying pathogenic mechanisms are still being studied, but it is known that obesity-related metabolic changes are found in asthma.

Research is ongoing worldwide to establish the contribution of MetS and obesity to the increased risk of developing asthma. It has now been established that various cell types, including vascular endothelial cells, renal epithelial cells and glandular epithelium, can be altered in MetS. It is unknown, but there is a high degree of probability that patients with MetS have altered airway epithelium or subepithelial function [13, 14].

In their study, Camargo et al. found a link between asthma and three components of the metabolic syndrome, namely obesity, hypertension, and fasting glucose/diabetes [15]. In addition, a direct correlation was found between body mass index (BMI), but not MetS itself. Thus, the key risk factors linking MetS and AD are abdominal obesity, insulin resistance (high glucose levels), and hypertension [15, 16].

Therefore, the study of the comorbid course of asthma and MetS is an urgent issue in the modern clinic of internal medicine. **The problem difinition** of this study was to highlight certain issues of comorbidity of asthma and metabolic syndrome in adult patients.

Methodology/Approach.

According to the study design, n=94 patients with a diagnosis of asthma were included according to the inclusion/exclusion criteria, namely: the evidence-based clinical practice guideline 'Bronchial Asthma' [17] and taking into account the recommendations of the International Global Initiative for the Diagnosis and Treatment of Asthma (GINA). [18]. Inclusion criteria were: informed consent to participate in the study, patients aged 18-60 years, persistent asthma of varying severity. Exclusion criteria: refusal to participate in the study, acute infection, acute somatic pathology and decompensation of any somatic comorbidity, endocrinological obesity, cancer, mental disorders, COPD, asthma in the acute stage.

The study was randomized. Patients were allocated to groups by simple randomization with stratification elements and were conducted on the basis of the departments of general practice of family medicine and outpatient therapy and in collaboration with the department of propaedeutics of internal medicine and therapy of Odesa National Medical University.

The severity of asthma was determined in accordance with the consensus documents, namely:

- mild asthma is asthma that is successfully controlled with treatment according to Step 1 or 2, for example, with the use of short-acting β-2-agonists as monotherapy, or with the addition of low doses of controlling drugs (low doses of ICS, leukotriene receptor antagonists or chromones);
- moderate asthma is asthma that is successfully controlled with treatment according to step 3 (e.g. low-dose ICS/ long-acting BATDs).
- severe asthma is asthma that requires treatment according to step 4 or 5 (e.g. high-dose ICS/ABA) or treatment to maintain good symptom control and reduce the risk of exacerbations.

Diagnosis of metabolic syndrome was performed in accordance with current regulatory documents [19] (Table 1).

Patients were offered a comprehensive physical and laboratory-instrumental examination, including: anamnesis; anthropometric examination (determination of body weight, height, BMI, percentage of body fat and muscle mass); physical examination; fasting plasma glucose, lipid profile, blood pressure measurement for at least 2 weeks 2 times a day with diary keeping; spirography. Additionally, patients filled out the Asthma Control Test [20].

Blood glucose levels were measured according to generally accepted methods using a Cobas 6000 analyzer (Roche Diagnostics, Switzerland).

The study of lipid spectrum, namely high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG), was performed by enzymatic colourimetric method from patients' venous blood, which they took on an empty stomach using a Cobas 6000 analyzer; Roche Diagnostics (Switzerland).

Anthropometric measurements (height, body weight) were performed, BMI was calculated, and impedance measurement was performed using a bioelectric impedance meter OMRON BF 51 (Japan), which was used to determine the percentage of body fat and muscle mass.

Spirography was performed as a routine procedure according to the recommendations of the American Thoracic Society/European Respiratory Society (ATS/ERS) using an Alpha spirograph (Germany). Positive response to bronchodilator (BD) (reversibility test): increase in FEV1 by > 12% and > 200 ml. The three best characteristics were selected. The average of the three was taken as the patient's final value.

Statistical processing of the results was performed using parametric and nonparametric analysis methods of HSPSS Statistica 2.0. In the comparative analysis of independent groups, the Student's test was used for unpaired samples (subject to homoscedasticity and normal distribution of data) and the Mann-Whitney test (for heteroscedastic data with a different type of distribution). The relationship between the features was studied using Spearman's correlation analysis (r), and Pearson's χ^2 criterion was used to assess the relationship between qualitative and quantitative features.

Results.

According to the study design, n=94 patients with a diagnosis of asthma participated in the study. The average age of the patients was 36,24±2,34 years, of whom n=52 were women (55,00%) and n=42 were men (45,00%).

The anamnesis revealed that the majority of patients complained of cough (n=59; 62,77%), sputum production (n=47; 50,00%), shortness of breath (n=48; 51,06%), wheezing (n=38; 40,43%), and chest tightness (n=25; 26,60%). The majority of patients associated the onset of asthma with an episode of acute upper respiratory tract infection, and the mean duration of asthma was 7,04±0,5 years.

Patients included in the study had different severity of asthma, so out of 94 patients, n=31 patients (32,98%) had mild asthma, n=46 (48,94%) had moderate asthma, and n=17 (18,09%) had severe asthma.

The patients underwent an anthropometric examination, the results of which are presented in Table 2.

Table 2

Anthropometric parameters in the examined patients depending on the severity of asthma

Proceedings	**BMI, kg/m^2**	**Body weight, kg**	**fat mass, %**	**Muscle mass, %**
Light	26,25±08,05*	82,36±2,52*	31,37±1,54*	28,24±0,87
Middle	29,41±1,62	92,84±1,45	38,34±1,47	27,12±0,45
Heavy	33,26±1,09	95,32±2,51	43,54±1,26	25,42±0,44

Note: *p≤0,05

Patients were divided according to the severity of asthma (Table 2). Comparative analysis of the results revealed a tendency for more severe asthma in patients with higher BMI, percentage of body fat, and lower percentage of body fat. The next step was a correlation analysis of these indicators, which revealed a direct positive relationship with the severity of the course (ρ=0,89, ρ=0,90; ρ=0,87, r=0,88; r=0.91, r=0,90, respectively).

In addition, other components of MetS, in addition to overweight or obesity, were analyzed. The results are presented in Table 3.

Table 3

Laboratory and instrumental components of metabolic syndrome in the examined patients depending on the severity of bronchial asthma

Proceedings	Glucose (mmol/l)	Triglycerides (mmol/l)	HDL (mmol/l	Blood pressure (mmHg)	
				Systolic	Diastolic
Light	5,2±0,87	2,16±0,51	1,02±0,09	135,13±3,45	82,34±2,31
Middle	5,1±0,73	2,25±0,13	1,14±0,13	138,62±2,67	81,58±4,31
Heavy	5,2±0,88	2,31±0,47	1,10±0,16	145,54±4,31	82,13±3,24

Note: *p≤0,05

A comparative analysis of other components in patients with MetS and asthma revealed a direct correlation between elevated TG levels and blood pressure (ρ=0,81, r=0,83; ρ=0,84, r=0,82, respectively).

The calculation of the number of patients with asthma according to the components of MetS is shown in Fig. 1.

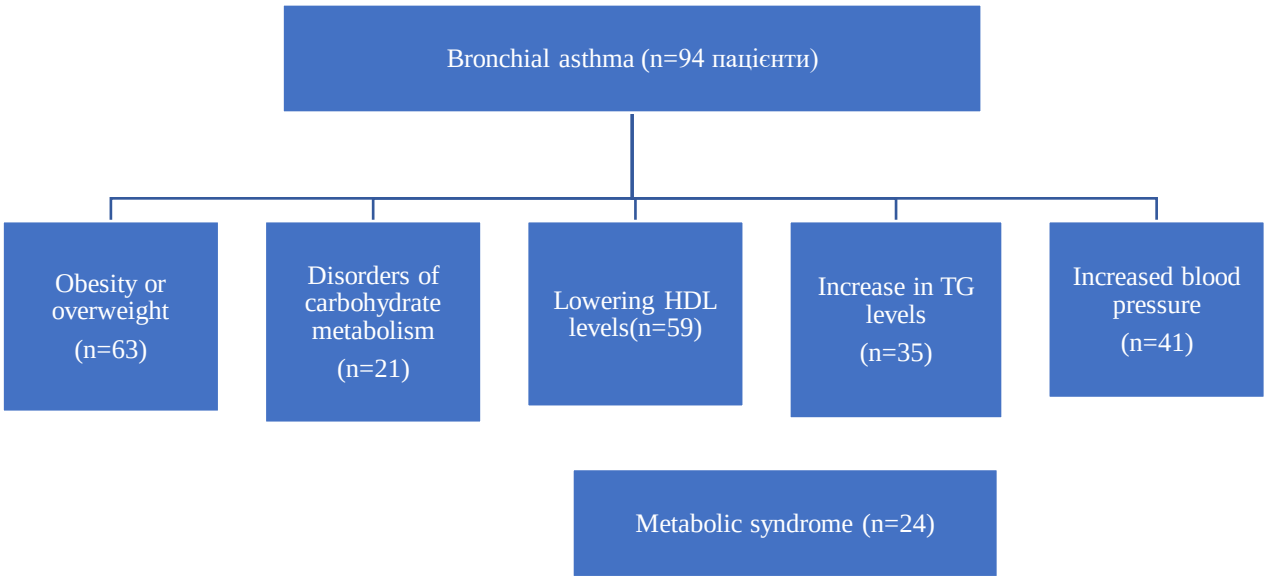

Fig. 1. Distribution of patients with asthma according to the components of the metabolic syndrome

Figure 1 demonstrates that the majority of patients with asthma had obesity or overweight as a comorbidity of asthma. The smallest number of patients had carbohydrate metabolism disorders. Thus, n=21 (22,34%) patients had elevated fasting plasma glucose levels, and n=24 (25,53%) patients out of all the subjects had MetS and asthma.

All patients were interviewed using the Asthma Control Test questionnaire to determine asthma control. The analysis of the results revealed that most patients had a controlled course of asthma with the absence of clinically significant symptoms, while patients with MetS in the setting of asthma had the lowest asthma control scores (Fig. 2).

The results showed that patients with MetS had the lowest level of asthma control (Fig. 2), with a score of 15.3±0.12 (p≤0.05). Patients with certain comorbidities had higher scores, as shown in Fig. 2. However, these scores did not reach statistical significance (p≤0,05).

In accordance with the study design, a comparative analysis of spirography parameters in patients with and without MetS was performed. The data are presented in Table 4.

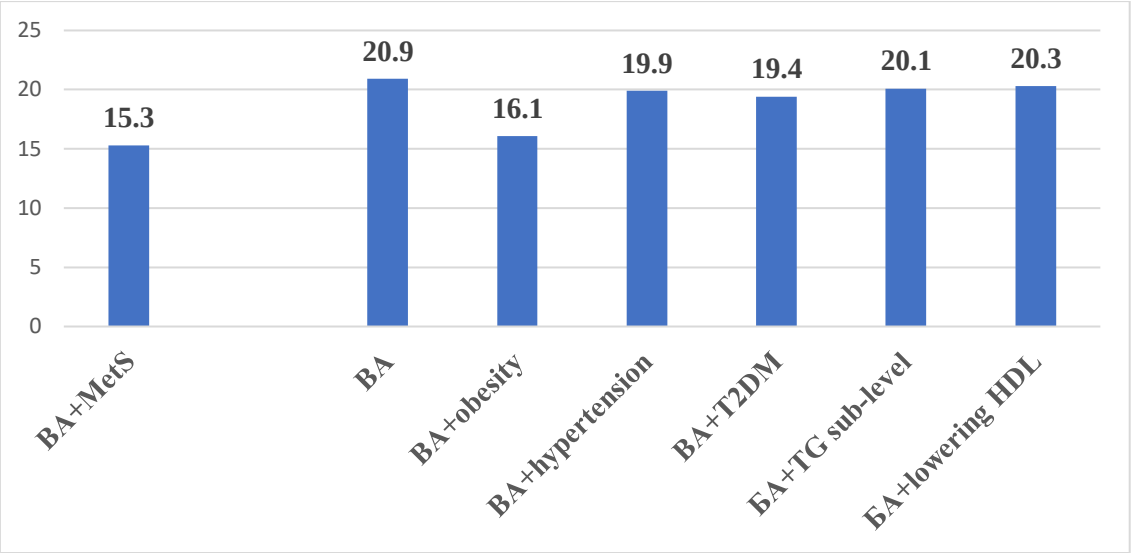

Fig 2. Control of asthma in patients with different components of the metabolic syndrome according to the AST questionnaire

Table 4.
Results of spirographic examination in the examined patients

Indicator	Bronchial asthma + Metabolic syndrome			Bronchial asthma without metabolic syndrome		
	Light	Middle	Heavy	Light	Middle	Heavy
VC, %	92,34±1,31	73,14±1,35*	55,14±1,27	93,25±1,75	79,45±1,19	56,18±1,25
FVC, %	75,56±0,97	65,82±1,91*	48,26±1,92	75,16±1,13	77,53±1,52	49,35±1,71
FEV_1, %	88,14±1,95	66,45±1,25	44,26±1,53	87,54±1,54	70,82±1,34	46,25±1,34
FEV_{1R}, %	91,45±1,99	81,76±1,01*	69,73±1,57	89,45±1,13	91,53±1,98	67,26±1,32
FEV_6, %	84,89±1,16	72,56±1,73	49,34±2,51	89,67±0,69	71,67±2,36	50,12±1,67
PEF %	91,22±2,15	60,26±1,41*	47,36±1,28	89,76±1,45	69,12±3,57	47,89±1,15
FEF_{25-75}, %	97,17±1,16	69,26±2,87	43,74±2,53	95,26±1,76	64,32±1,89	44,04±1,98
FEF_{25}, %	81,68±2,67*	59,85±2,06	44,52±2,78	69,46±1,98	64,53±2,15	45,47±1,81
FEF_{50}, %	82,17±1,84	60,88±1,52	41,76±1,91	83,17±1,57	61,64±3,76	41,04±1,14
FEF_{75}, %	102,00±4,89	61,35±2,74	42,63±2,70	101,56±3,68	49,50±6,48	43,45±2,54

Note: * – $p<0,05$.

The results demonstrate that patients with asthma + MetS had significantly lower spirogram scores ($p<0.05$), but only in patients with moderate asthma ($p<0.05$), which is not explained in the current study, but is the basis for further substantiation in the future.

Discussion.

The results obtained are in line with international experience regarding the association of obesity and severe asthma.

Systemic inflammation is one of the components of MetS and asthma, so a more severe course of asthma in a comorbid patient is expected. Determination of personalized tactics for the management of patients with comorbidities is an urgent issue in the modern clinic of internal medicine.

We have evaluated individual components of MetS, and the data obtained confirm previous observations that established the relationship between asthma and metabolic changes in patients [13, 21]. For example, insulin resistance causes abnormal muscle fat metabolism and reduces glucose utilization [22, 23]. Similar findings were also obtained in a study conducted by Assaad et. al. that reported the prevalence of MetS in patients with a history of asthma [24].

A comparative analysis of the spirographic study data revealed that patients with asthma + MetS had statistically significant differences ($p<0.05$).

The analysis of anthropometric data revealed that patients with the highest BMI and body weight had a significantly more severe course of asthma ($p<0,05$), which is consistent with the data of available world studies [24, 25], and a positive correlation was found between BMI, percentage of body fat and lower percentage of body fat in patients with severe asthma ($\rho=0,89$, $\rho=0,90$, $\rho=0,87$; $r=0,88$, $r=0,91$, $r=0,90$, respectively).

The data obtained indicate the need for individual management of patients with comorbidities, including MetS and asthma, to prevent severe asthma, which is associated with inadequate asthma control and poor quality of life.

Conclusions.

- BMI, percentage of body fat have a direct close correlation with a lower percentage of body fat in patients with severe asthma ($\rho=0,89$, $\rho=0,90$, $\rho=0,87$; $r=0,88$, $r=0,91$, $r=0,90$, respectively).

- A comparative analysis of the subjective assessment of asthma control by questioning over the past 4 weeks (ACT test) revealed that the lowest level of control was in patients with MetS, namely 15.3 ± 0.12 points ($p<0.05$).

- Patients with combined asthma and MetS had significantly lower spirogram scores ($p<0.05$).

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