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Clinical-pathogenetic peculiarities of diabetes mellitus type 2 in patients with asthma

Key words: *bronchial asthma, diabetes mellitus type 2, cytokines, matrix metalloproteinase-9, monocyte chemoattractant protein-1.*

The problem of comorbidity belongs to the most important ones in internal medicine [11]. Coexistence of several diseases changes the course of each of them, facilitates an earlier formation of complications and creates difficulties for therapy [2]. Asthma is significantly widespread in the world and in Ukraine [3]. The number of patients with asthma is steadily rising, also increasing is the part of cases with a combination of asthma and diabetes mellitus type 2 (DM2T) [10; 14; 19]. It should be noted that some endocrine disturbances, such as DM2T and obesity, may affect the course and complications of asthma [5; 9]. The risk of development of DM2T in asthma patients varies from 1.3 to 2.1 [16; 18; 22]. The conducted researches for studying an association of asthma, DM2T and obesity demonstrated a close relationship between obesity, asthma and DM2T [8; 19].

Diabetes mellitus (DM) is often associated with a reduced pulmonary function and a lower forced expiratory volume (FEV) rather than only with abdominal obesity, arterial hypertension and different cardiovascular diseases [12; 13; 18]. Metabolic syndrome and DM2T on the one hand and an obstructed airway conductance with a reduced pulmonary function on the other hand can mutually potentiate each other [11; 20]. A combination of carbohydrate metabolic disturbances and asthma can be caused by both genetic mechanisms, development of an inflammation, formation of an energy failure in tissues and basic therapy for bronchial obstruction with glucocorticosteroids [4; 17].

A significant part in the development of a persisting inflammation of the respiratory tract in patients with asthma and smooth muscle hyperplasia depends upon the state of the immune system. Besides, some part in the development and maintenance of the inflammation in the bronchial wall is also played by epithelial cells, fibroblasts and vascular endothelial cells. In the process of activation all these cells release/produce a large variety of biologically active substances (leukotrienes, cytokines, chemotactic factors, thrombocyte activation factor, etc.). Interleukin (IL) system disorders, the roles of matrix metalloproteinase-9 (MMP-9) and monocyte chemoattractant protein-1 (MCP-1) in the process of remodelling of the respiratory tract in case of a combination of asthma and endocrine pathology are debated very vigorously [1; 22].

Aim. Revealing of peculiarities in clinical and pathogenetic manifestations of asthma with an uncontrolled course of the disease in combination with DM2T.

Materials and methods. The study involved 55 patients, who were divided into 2 groups. Group I included patients with isolated asthma (n = 20), group II had asthma with DM2T (n = 35). The patients underwent a general clinical examination, a physical examination and revealing of their anthropometric values: weighing, calculation of their body mass index (BMI), measuring of their waist circumference (WC) and hip circumference (HC). Their respiratory function (RF) was assessed. All patients underwent assessments of their fasting blood glucose level, insulin level and HOMA-IR index. The content of MMP-9 and MCP-1 in blood serum were determined by the method of enzyme immunoassay (ELISA) with help of HUMAN MMP-9 and HUMAN MCP-1 kits (eBioscience, Austria). IL-8 and IL-12 were quantitatively determined using BEST-IFA immunoenzymatic test systems (Vector-Best, Ukraine).

The study findings were statistically processed with use of SPSS19 program for Windows (IBM, USA). Quantitative variables were described by the following parameters: the median (Me) and the 25th and 75th percentiles (M [25%; 75%]). In order to reveal differences between independent samples, the Mann–Whitney U test was used. The normality of data

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distribution was analysed with help of the Shapiro–Wilk test. Relations between the indices were studied with a correlation analysis using the Spearman's rank correlation coefficient (r) and the Chaddock's scale.

Results

Interpreting different mechanisms of pulmonary dysfunction, we found out that only the obstructive type of the damage was diagnosed in 20 cases (100%) from group I. In group II, 6 patients (19.3%) revealed the restrictive type, 13 (41.9%) had the obstructive one and there were 12 (38.8%) with the mixed type of ER dysfunction.

Hence a reliable advantage of the obstructive ($p < 0.001$) and mixed ($p < 0.001$) types of ventilation disorders in the above patients versus group I can be caused, as some authors believe, by mechanical effects of abdominal obesity owing to a reduced excursion of the diaphragm and thorax rather than only by a spasm of smooth muscles of the bronchi, a deformity of the bronchi and their expiratory collapse [9]. According to the obtained results during BMI studies, cases from group I had the normal weight – their BMI averaged 22.0 [21; 22.7], while in group II there were 15 (42.8%) patients with an extreme body weight and 20 (57.2%) patients with the 1st degree of obesity, it averaging 28.5 [26.7; 32.15] for the whole group. Our correlation analysis in patients from group II revealed a marked significant correlation between the age and WC/HC ratio ($r = 0.52$, $p < 0.001$), this fact demonstrating increased fat depots during their lifetime in patients from this group, and between FEV1 and BMI $r = –0.63$ ($p < 0.001$), thereby showing a negative effect of obesity on the pulmonary function [6].

It is known that development of various complications of DM2T is connected with its duration [15]. In order to find out possible relationships between the duration of DM2T and development of ER dysfunctions a correlation analysis was made. We revealed a decrease of FVC depending upon the disease duration and FEV1 in asthma patients having DM2T, $r = –0.38$ ($p < 0.001$) and $r = –0.54$ ($p < 0.05$), according to FEV1/FVC index, $r = –0.43$ ($p < 0.05$). In group I, any statistically significant relationship between the correlation coefficient and duration of the disease was absent.

We revealed a statistically significant correlation relationship between the value of FEV1 and the level of HbA1c. The correlation coefficient was as follows: in group I, $r = –0.12$ ($p < 0.08$); in group II, $r = –0.49$ ($p < 0.001$). Changes in values of FEV1 depending upon the glucose level in patients with DM were also revealed in another research, Framingham Offspring Cohort [22]. At the same time some researchers did not reveal any considerable changes of FEV1 in comparison of patients with and without DM [6]. But an effect of a pathologically high glucose level is doubtless.

We revealed a statistically reliable relationship between the FVC value and the level of HbA1c in patients from group II ($r = –0.50$, $p < 0.05$).

The content of IL-8 and IL-12 in patients from group II was increased, respectively, by 30.6 and 33.2 times versus group I. A high level of proinflammatory cytokines of IL-8 and IL-12 (Me = 134.8 pg/ml and 255.6 pg/ml, respectively) in case of an uncontrolled course in asthma patients having DM2T at the phase of exacerbation demonstrates persistence of the chronic inflammatory process, the latter being the essence of both asthma and DM2T. The participation of such inflammatory markers as MCP-1 and MMP-9 in the inflammatory process in cases from the above group forms an unfavourable background for progression of the disease and

Table

Results of the studied indices (median [Me], percentiles [25%; 75%]) in patients with asthma and asthma+DM2T

Indices	asthma, n = 20			asthma+DM2T, n = 31			Statistics, Mann-Whitney U test	Significance, P
	Median	Percentiles		Median	Percentiles			
		25	75		25	75		
IL-8, pg/ml	4.11	3.83	4.63	134.80	132.05	146.65	0	0.001
IL-12, pg/ml	9.99	9.40	10.39	255.60	234.55	305.55	0	0.001
MCP-1, ng/ml	51.83	49.89	53.61	806.14	768.36	904.37	0	0.001
MMP-9, ng/ml	35.35	32.84	37.62	786.50	386.14	933.31	0	0.001
FVC,%	98.00	97.00	99.00	66.54	54.25	73.75	255	0.001
FEV_1,%	95.00	94.00	95.00	56.72	43.50	61.75	310	0.001
FEV_1/FVC	82.00	81.00	83.00	70.13	62.00	78.62	482	0.001
HbA1c,%	4.24	3.85	4.56	7.41	6.81	9.23	0	0.001
Insulin, mU/l	8.23	6.90	10.17	17.57	14.63	20.20	0	0.001
Glucose, mmol/l	4.30	4.09	4.54	8.62	7.32	10.20	0	0.001
HOMA-IR index	1.48	1.27	2.11	6.91	5.11	8.15	0	0.001
BMI	22.00	21.00	22.75	28.50	26.70	32.15	5	0.001

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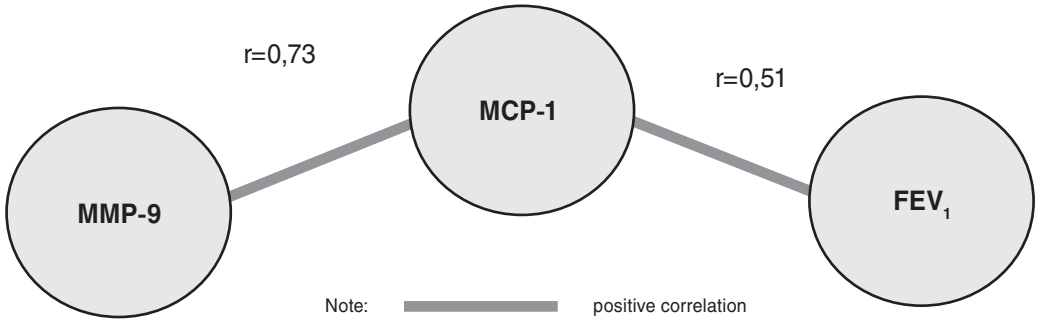

Fig.1. Correlations between MCP-1, bronchial obstruction and MMP-9 in patients with asthma and DM2T

development of remodelling of the bronchi. This fact confirms the revealed relationship between MCP-1 and the mediator of the antifibrosis system MMP-9 ($r = 0.73$, $p < 0.05$), which takes part in a cascade of mechanisms with the resultant diffuse chronic inflammation, thickening and hyalinosis of the basal membrane and sclerosis of interalveolar septa. Patients from group II revealed a direct relationship between MCP-1 and total FEV1 ($r = 0.51$, $p<0.05$) (Fig. 1). That is progression of bronchial obstruction in asthma patients having DM2T is associated with a proportional increase of the fibrotic marker MCP-1.

The obtained results reveal that an extreme concentration of MCP-1 as the fibrosis marker in asthma cases having DM2T during progression of signs of bronchial obstruction is suppressed by a proportional increase of the fibrolysis indicator MMP-9, this fact being in favour of adaptive responses in the above group of patients.

Conclusions

1. It has been revealed that the presence of signs of extra weight and obesity in patients with asthma and DM2T leads to a deterioration of the respiratory function of the lungs versus the corresponding indices in asthma cases without comorbidity.

2. Patients having asthma combined with DM2T reveal external respiratory dysfunctions in the form of lower values of FEV1/FVC and FEV1 versus the corresponding indices in asthma cases without comorbidity.

3. Relationships between the level of proinflammatory cytokines (IL-8, IL-12) and that of MMP-9 and MCP-1 were revealed.

The consideration of asthma and DM2T as a chronic autoimmune inflammation creates the basis for a more thorough study of the common links in the pathogenesis of asthma and DM2T that can cause their coexistence and formation of mutual aggravation syndrome.

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