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ASTHMA AND DIABETES MELLITUS 2 TYPE – POLYMORBIDITY OF THE XXI CENTURY

Key words: *asthma, type 2 diabetes mellitus, bronchial obstruction, glomerular filtration rate.*

Recently, the issue of heterogeneity of the disease began to be paid attention in the "Recommendations of the Global Initiative for Asthma Strategy" (Revision 2016) [5]. The document considers both heterogeneity of clinical manifestations of asthma, and their response to therapy. In this case, this phenomenon is often described from the point of view of so-called "phenotype" and even "subphenotype" of asthma which is known as a set of characteristics arising as a result of the interaction between the genetic properties of the organism and the environmental factors [3, 6, 7]. This is especially important if you consider the genetic affinity of the kidneys and lungs. In addition, according to the authors, hyperventilation, hypoxemia, acidosis in cases of exacerbation or severe persistent disease lead to the impairment of kidneys [1, 2, 9]. Microalbuminuria, which is associated with hypoxia, may be relevant [7, 8]. Experimental and clinical studies have demonstrated different positions regarding the impact of obesity and type 2 diabetes mellitus (DM2T) on the development of asthma. Mutual influence of asthma, DM2T and obesity is traditionally explained by four groups of factors: genetic, mechanical, hormonal and inflammatory [2].

It is known that the kidneys and lungs provide the maintenance and immutability of the basic physico-chemical constants of the internal fluid: acid-alkaline and water-osmotic state regulation, etc. It is entirely anticipated that lung function impairment may affect the function of kidneys [1, 5, 10]. It is obvious that in patients with DM2T all types of metabolic processes and adaptive-regulatory mechanisms of homeostasis are impaired. The most frequent manifestations of the kidney damage in patients with obesity and DM2T are microalbuminuria, proteinuria, hyperfiltration and glomerular filtration disorders dysfunction of the kidneys [6, 9]. Severe, uncontrolled and prolonged course of asthma leads to a decrease in the glomerular filtration rate (GFR) which develops as a result of the depletion of the compensatory capacity of the kidneys to maintain effective filtration pressure due to persistent renal blood flow disorders. The deterioration of the conditions of glomerular filtration in the future can cause significant renal dysfunction and worsening of the prognosis in patients with severe asthma in combination with type 2 diabetes and obesity.

The **aim** of the study is to analyze metabolic disturbances and velocity of glomerular filtration rate in patients with asthma in combination with type 2 diabetes mellitus.

Materials and methods

The work was performed on the basis of the clinic communal health care institution "Emergency Medicine Center", which is the clinical base of the Department of Propedeutic of internal medicine №2 and the nursing care of the Kharkiv National Medical University and on the clinical base of the communal health care institution of "Kharkiv city hospital №13". 105 patients with asthma in combination with DM2T (main group) and 62 patients with isolated asthma (comparison group) were examined. All investigated patients suffered from uncontrolled moderate asthma. The average age of the patients was 54.32 [46.50; 60.95] years old, while in the control group — 48.0 [36.0; 53.0]. The control group consisted of 21 practically healthy persons of the same age and sex. The diagnosis of diseases was carried out in accordance with branch standards regulated by the orders of the Ministry of Health of Ukraine No. 128 dated March 19, 2007 "On Approval of Clinical Protocols for the Provision of Medical Aid in the Specialty" Pulmonology"; № 868 dated 08.10.2013 "On Approval and Implementation of Medical-Technological Documents for the Standardization of Medical Aid in Asthma". The diagnosis and treatment of concomitant DM2T was carried out by a qualified endocrinologist in

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accordance with the acting Ukrainian protocols (Order of the Ministry of Health of Ukraine dated December 21, 2012, No. 1118). The diagnosis of DM2T was made in accordance with the combined recommendations of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) as for the regarding diagnostic criteria for diagnosis of diabetes. Target indicators for the treatment of patients with diabetes were given by EASD 2013. To control the carbohydrate metabolism in the blood serum, glucose levels were determined on the basis of by the enzymatic colorimetric method with deproteinization (Olvex Diagnosticum, Russia) and glycated hemoglobin (HbA1c) by means of biochemical techniques taking into account the reaction with thiobarbituric acid. The concentration of insulin in the blood serum was defined using "Insulin ELISA" ("DRG Diagnostics", Germany) kits with the help of a in solid-phase radioassay. Insulin resistance was determined using the model HOMA-IR = insulin concentration (μd / ml) × glucose (mmol / L) / 22.5. The velocity of glomerular filtration rate was calculated according to the nomogram for the calculation of GFR based on the level of creatinine in the blood serum, with the regard of to sex, age and race using the formula CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). The CKD-EPI formula is recommended as a screening method for GFR evaluation (KDIGO, 2013, National Recommendations: Chronic Kidney Disease, 2012). The study evaluation of the lipid profile parameters of the lipid profile covered included the determination of total cholesterol (TCH), triglycerides (TG), high density lipoprotein cholesterol (HDL) by enzymatic method using sets of reagents Olvex Diagnosticum (Russia). Low Cholesterol content of low density lipoproteins (LDL) was calculated by the formula of W. T. Friedewald (1972). Statistical data processing was performed by means of the SPSS statistical software package (version 17.0 for Windows; SPSS, Chicago, IL). To describe and compare the indices whose distribution differed from normal, nonparametric methods were used: computation of the median and interquartile range Me [25; 75]; Mann-Whitney criterion. Correlations were estimated by the Spirman (R) correlation coefficient and the Chaddock scale.

Results of research and discussion

When studying the parameters of external respiration (ER), in all the patients the volume and speed indices were reduced. FEV_1 in the patients of the main group was 50.75 [44.75; 59.00]%, in the patients of the comparison group — 56.00 [44.50; 69,10]% ($p > 0,05$); which ,compared to the control group, had a significant difference ($p < 0,001$) in comparison with control group. When comparing the speed indicators at the level of FEF_{25}, FEF_{50}, and FEF_{75}, there was a significant difference in the patients between the groups ($p < 0.05$). The analysis of GFR revealed a decrease of this indicator parameter in two groups of the patients in relation to the compared with control group ($p < 0.05$). In the patients of the main group it was 53.40 [49,73; 60.79] ml / min / 1.73 m^2, that was 2.2 times lower than in the control group and 1.2 times lower fewer than in the comparison group ($p < 0.05$). Significant differences testify to a kidney function abnormality in the patients under study; namely, their perfusion properties. Hypoxemia, present in a moderate asthma, may be mediated by renal dysfunction [2, 9].

To confirm this fact, we obtained positive correlation interactions of different strength in the investigated groups of the patients between the speed indicators and GFR: FEV_1 and GFR ($R = 0.41$; $p < 0.05$; $R = 0.39$; $p < 0.05$) respectively, and between FEF75 % and GFR ($R = 0.55$; $p < 0.05$; $R = 0 , 37$; $p < 0.05$) respectively. The decrease in GFR in the patients of the main group was accompanied by microalbuminuria, which amounts 72.00 [30.00; 130.00] mg / l ($p < 0.001$). In the comparison group microalbuminuria was absent.

In the distribution of patients, depending on the violation of FEV_1, 3 subgroups were formed ($FEV_1 < 50$ %, $50\ \% \le FEV_1 \le 60$ %, $FEV_1 > 60$ %) and 3 subgroups with depending on the violation of GFR (GFR < 60, ml / min / 1.73 m^2, $60 \le GFR < 90$, ml / min / 1.73 m^2 and GFR ≥ 90, ml / min / 1.73 m^2). With the progression of bronchial obstruction in the patients of the main group, the probable differences in the HOMA-IR index, depending on the syndrome of bronchial obstruction, were detected. HOMA-IR was maximally raised in the patients with FEV1 < 50 % in both groups ($p < 0.001$), which coincided with atherogenic disorders. According to the results of our research, atherogenic dyslipidemia was discovered in all the examined patients, mostly due to hypertriglyceridemia. When analysing lipid metabolism indices in patients with asthma + DM2T with the syndrome of bronchial obstruction, a high level of significance of TCH, TG and LDL CH was observed between the subgroups $FEV_1 \le 50$ % and $50\ \% \le FEV_1 \le 60$ % ($p < 0.05$). In the subgroup $FEV_1 < 50$ %, the rates were the highest, indicating the development of hypoxia, which contributes to the development of atherogenic changes in patients with asthma with and type 2 diabetes. Sizable differences were found in the patients of the main group with $50\ \% \le FEV_1 \le 60$ % ($p < 0.05$) compared to the control group according to the parameters of THC, TG and LDL. In the correlation analysis between $FEV_1 < 50$ % and the level of lipids — THC, LDL, and TG — in the patients of the main group the inverse association feedback was revealed ($R = -0.31$; $p < 0.05$; $R = -0.42$; $p < 0 , 05$, $R = -0,54$; $p < 0,05$) and TG in the patients of the comparison group ($R = -0,39$; $p < 0,05$).

As the bronchial obstruction syndrome progressed, an increase in the level of insulin and the HOMA-IR index was observed. In the patients with FEV1 < 50 %, HOMA-IR was lower than in the patients with $FEV_1 > 60\%$ ($p < 0.001$).

Conclusions

1. Comorbidity of bronchial asthma with type 2 diabetes is accompanied by a cascade of metabolic disorders, which are manifested as probable changes in carbohydrate and fat metabolism indices. The reverse correlation changes were found in the patients of the main group between FEV_1 and BMI ($R = -0.55$ $p < 0.05$;), between HDL and insulin ($R = -0.36$, $p < 0.05$), the index HOMA- IR and LDL ($R = -0.37$).

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2. In patients with moderate asthma of moderate disease course kidney failure develops in 15.4 % of cases; with a combination of type 2 diabetes - up to 63.56 %. Kidney impairment is manifestsed by microalbuminuria progression in patients with asthma with and type 2 diabetes mellitus in 42.31 %. Violation of the renal filtration function of the kidneys in the group asthma + DM2T — 53.40 [49,73; 60.79] ml / min / 1.73 m^2. Violation Decrease of glomerular filtration rate is accompanied by progression of bronchial obstruction syndrome in patients with asthma with type 2 diabetes mellitus ($p < 0.05$).

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Abstract

Aim. To analyze metabolic disorders and glomerular filtration rate (GFR) in patients with asthma in combination with type 2 diabetes mellitus (DM2T).

Materials and methods. 105 patients with asthma in combination with DM2T have been investigated as main group, 62 persons with isolated asthma as comparison group. All examined patients had uncontrolled asthma of moderate severity. The control group consisted of 21 healthy individuals. The respiratory function, GFR, carbohydrate and lipid metabolism and insulin resistance were determined.

Results. The decrease of volumetric and high-speed indicators of external respiration function and GFR ($p < 0.001$) in all investigated patients was revealed. Correlational relationships between FEV1 and GFR ($R = 0.41$; $p < 0.05$; $R = 0.39$; $p < 0.05$) were found in patients of the main and comparison group, respectively, and between FEF 75 % and GFR ($R = 0.55$; $p < 0.05$; $R = 0.37$; $p < 0.05$), respectively. The decrease in GFR in patients of the main group was accompanied by microalbuminuria ($p < 0.001$). In the comparison group microalbuminuria was absent. HOMA-IR was maximally raised in patients with $FEV_1 < 50$ % in both groups ($p < 0.001$), which coincided with atherogenic dyslipidemia.

Conclusions. Uncontrolled asthma of moderate severity, both isolated and in combination with type 2 diabetes, is accompanied by a cascade of metabolic disorders, which manifest by significant differences in carbohydrate and lipid metabolism indices, decline in glomerular filtration rate and progression of the bronchial obstruction syndrome between themselves and with the control group.

Key words: asthma, type 2 diabetes mellitus, bronchial obstruction, glomerular filtration rate.

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