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RESEARCH ARTICLE

THE ROLE OF MDR1 (C3435T) GENE POLYMORPHISM IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE ASSOCIATED WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Chronic obstructive pulmonary disease is a multifactorial disease characterized by gene-gene interaction as well as environmental effects. The incidence of type 2 diabetes mellitus with chronic obstructive pulmonary disease is proved to be higher than in case of its absence.All the patients were divided into two groups. The first group included 53 patients with chronic obstructive pulmonary disease. The second group included 49 patients with chronic obstructive pulmonary disease with comorbid type 2 diabetes mellitus. CAT test, 6-minute walk test, BODE integral index, spirometry, bioimpedansometry were used for examination. Lipid spectrum, carbohydrate metabolism, endothelial functional status, leptin, adiponectin and serum levels were also determined by means of enzyme immunoassay. The results of our study showed that there is no significant difference between the genotypes of the control group of healthy individuals and patients with chronic obstructive pulmonary disease and comorbid type 2 diabetes mellitus. Though, certain association of this gene polymorphism with clinical findings by CAT-test, certain parameters of carbohydrate (fasting glucose) and lipid metabolism (total cholesterol and low density cholesterol lipoproteins), endothelial functional state (nitrate / nitrite level) with minor allele T available is found. Further investigation is required and possible use of the findings obtained to be implemented in personalized treatment in case of comorbidity of chronic obstructive pulmonary disease and type 2 diabetes mellitus, taking into account MDR1 (S3435T) gene polymorphism.

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INTRODUCTION

COPD is known to be a multifactorial disease (Rabe, 2017) characterized by gene-gene interaction (Silverman, 2020), as well as environmental impact (Sarkar, 2019), but not all the mechanisms for the development and advance of this pathology have been fully understood. Development of chronic systemic inflammation is found to be the characteristic of COPD and the appearance of systemic effects (Hikichi, 2019), leading to an increased incidence of concomitant pathology (Barnes, 2017). The incidence of type 2 diabetes mellitus with COPD is proved to be higher than in case of its absence (Katsiki *et al*., 2019; Cazzola, 2017). The role of MDR1 gene (C3435T) polymorphism in the development and advance of COPD (8-9) has been studied, although the results of these studies are controversial. Multiple drug resistance gene (MDR1) is known to be localized in chromosome 7q21, and the products of this gene (multiple drug resistance protein-1 and resistance protein associated with lung) act as antioxidants, protecting the lung tissue from oxidative stress, toxins and poisons released when smoking cigarettes (Hikichi, 2019). This gene polymorphism has also attracted the attention of scientists in the study of mechanisms of development of type 2 diabetes mellitus (Rizvi, 2017). Although the results obtained are single and ambiguous, they can be used to correct lipid and carbohydrate metabolism disorders, taking into account pharmacogenetic aspects. Therefore, the study of MDR1 gene polymorphism associated with COPD and type 2 diabetes mellitus appears to be reasonable. The aim is to study the genotypes of MDR1 (C3435T) gene polymorphism and its relationship with clinical, instrumental, and laboratory parameters in case of chronic obstructive pulmonary disease associated with type 2 diabetes mellitus.

MATERIALS AND METHODS

53 patients with COPD and 49 patients with COPD with concomitant type 2 diabetes were examined during 2016-2019.

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All patients were in remission of the disease and met the criteria for inclusion and exclusion. COPD and type 2 diabetes mellitus were diagnosed according to international protocols. The studies meet the requirements of the Helsinki Declaration of the World Medical Association "Ethical principles for medical research involving human subjects as the object of study" opinion of the Commitie on bioethics as HSEE "Bukovinian State Medical University" №2/2016. The diagnosis and stage of COPD were established in accordance with the recommendations of GOLD 2017, by the Order of the Ministry of Health of Ukraine No. 555 of 27.06.2013 and changes to the Order No. 270 of April 16, 2014. The clinical characteristics of patients are illustrated in Table I.

CAT-test, 6-minute walk test, BODE integral index, and spirometry ("BTL08 SpiroPro" Spirograph (UK)) were used in the study, which included patients with COPD with an FEV1 / FVC ratio less than 0.7 and with II-m, III and IV degrees of bronchial obstruction according to GOLD spirometric classification. Bioimpedance analysis (BC-601 Portable Apparatus (TANITA, Japan) was used to assess body composition. The body weight, BMI, muscle mass, fat percentage, visceral fat level, % water in the body were determined. Blood lipid spectrum was examined for total cholesterol (TC), triglycerol (TG), low density lipoprotein (LDL) cholesterol, very low density lipoprotein (VLDL) and high density lipoprotein (HDL) cholesterol levels (PZCormay, Poland). Carbohydrate metabolism was studied by fasting blood glucose test, glycosylated hemoglobin (HbA1c), and insulin level. The level of glycemia was investigated by the glucose oxidase method using standard sets of reagents manufactured by NPP "Philitis Diagnostics" (Ukraine). Glycosylated hemoglobin was determined using a photocolorimetric method using a set of reagents manufactured by ErbaLachemas. r. o (Czech Republic). The level of immunoreactive insulin (IRI) was examined by enzyme-linked immunosorbent assay using DRG InternationalInc reagents (USA). The functional state of the endothelium was examined for the content of stable metabolites of nitrogen monoxide (nitrites / nitrates), endothelin-1 (ET-1) in the blood, the number of CCEE, the content of soluble adhesion molecule sVV-1 (1). The number of circulating endothelial cells in the blood was determined by J. Hladovec method (1978) in the modification by N. Petrischev and others (1999). Blood content of stable metabolites of NO (nitrites / nitrates) was investigated by L. C. Greenetal method (1982), ET-1 level - by enzyme-linked immunosorbent assay using "Biomedica Medizinprodukte Gmb Hand Co KG" reagents (Austria). sVCAM-1 was determined in serum by ELISA using BenderMedSystems reagents (Austria). Serum levels of leptin (Diagnostics BiochemCanadaInc, Canada), adiponectin (Assay, USA) and resisting (Mediagnost, Germany), TNFα and TGFβ1 (Bender Med Systems GmbH, Austria) were determined using enzyme immunoassay kits. Serum CRP levels were determined according to the instructions (Humatex CRP "HUMAN", Germany).

Genomic DNA was isolated from the peripheral blood for molecular genetic studies. Genotyping of the polymorphic variant C3435T of MDR1 gene was done according to the protocol of Turgut S. *et al*. Two-sided Pearsonah-square test ($\chi 2$) was used to estimate the distribution of genotypes and alleles between groups. The calculations were performed using Statistica software, version 10.0 (Stat Softinc, USA).

RESULTS

The frequency of the genotype of MDR1 gene (C3435T) polymorphism in control and COPD patients without and with comorbid type 2 diabetes mellitus is presented in Table II. There were no differences between the genotypes in the presented groups. The analysis of bioimpedansometry indicators (Table III) demonstrated a significant difference between the group of COPD patients and COPD with concomitant type 2 diabetes mellitus in BMI, % fat, visceral fat, bone mass regardless of MDR1 gene polymorphism type 35 (C34). Muscle mass in these groups of patients was significantly different for genotypes SS and CT, in contrast to the genotype TT, which was not reliable ($p > 0.05$). Forced expiratory volume per second (FEV1) in both groups of patients had no significant difference and did not depend on the genotype of MDR1 gene polymorphism (C3435T).

When evaluating CAT test (Table IV), it was found that in the group of COPD patients with concomitant type 2 diabetes mellitus for TT genotype, the total score exceeded that one for SS genotype by 31.4% ($p < 0.05$). 6-minute walk test showed the difference between the COPD patient group and its comorbid course with type 2 diabetes mellitus in CT genotype (patients walked 23.1% less in the first group). BODE integral index was significantly higher in COPD patients with concomitant type 2 diabetes mellitus than that of CT genotype (28.7%, $p < 0.05$). The interpretation of the results of carbohydrate metabolism study (Table V) illustrated that in patients with COPD and comorbid type 2 diabetes mellitus, fasting glucose was significantly higher than that for TT genotype compared to SS genotype (18.9%, $p < 0.05$).

The level of total cholesterol (Table VI) in patients with COPD with concomitant type 2 diabetes mellitus was found to be significantly higher for the TT genotype (12.9%) compared with the group with the SS genotype ($p < 0.05$). LDL CL was also significantly higher in patients of the first group with the genotype TT compared with the genotype SS and CT (by 13.75 and 12.88%, respectively, $p < 0.05$). Analysis of systemic inflammation (Table VII) found that TNFα level was likely to be higher in COPD patients with concomitant type 2 diabetes mellitus, regardless of genotype. Although CRP level was higher in COPD patients with concomitant type 2 diabetes mellitus compared with the second group, the difference was in the SS genotype ($p < 0.05$) only. TGF was not significantly different between the two groups of patients. Serum leptin levels were significantly higher in COPD patients with concomitant type 2 diabetes mellitus, regardless of genotype. The level of resistin was probably higher in the latter group of patients than those with the SS and CT genotypes, but the TT genotype had no confidence between the two groups of patients. Adiponectin was significantly lower in COPD patients with concomitant type 2 diabetes mellitus in the presence of T allele. When examining endothelial functional status indicators (Table VIII), it was found that CCEE was significantly higher in the group of patients with COPD and comorbid type 2 diabetes mellitus regardless of genotype. However, the level of nitrates / nitrites in the first group of patients for the TT genotype was 41.5% lower compared to the SS genotype ($p < 0.05$). The level of ET-1 in patients with COPD with concomitant type 2 diabetes mellitus was significantly higher regardless of genotype. VCAM-1 levels were significantly higher in this group than for the SS and CT genotype ($p < 0.05$).

DISCUSSION

Certain scientists have evidenced the role of MDR1 (C3435T) polymorphism in the development and progression of COPD (Yücel, 2018). Thus, Turkish scientists have shown an association of the development of right ventricular dysfunction and oxidative stress with the T allele in COPD patients (Russo *et al*., 2019; Yücel *et al*., 2018). The role of this gene polymorphism in the development of type 2 diabetes mellitus is also studied (Rizvi *et al*., 2017). Thus, Yücel O. *et al.* were the first to study the relationship between MDR1 (C3435T) polymorphism and type 2 diabetes mellitus, as well as its effect on blood lipid levels. They showed that for this gene polymorphism no association of T allele with disease development and lipid dependence on genotype was detected. Although, they did not find any direct strong correlation between the level of lipids in patients with diabetes and MDR1 gene polymorphism (C3435T), they indicate that it is possible due to the complex effects of this polymorphism and the use of drugs that patients take regularly (Yücel, 2018). Rizvi S. *et al*. also studied the relationship of this gene polymorphism with carbohydrate and lipid metabolism in diabetic patients, and their findings confirmed previous results (Rizvi, 2017). According to the results of their study, there was no difference in genotypes between the groups of patients and the group of healthy individuals in the comorbid course of COPD and type 2 diabetes mellitus.

However, in case of association of MDR1 gene (C3435T) polymorphism in COPD patients with concomitant type 2 diabetes mellitus and clinical findings, in particular, according to the results of CAT test in the TT genotype patients obtained a higher number of points. Patients' exercise tolerance for 6-minute walk test was also lower in patients with comorbid pathology and had a significant difference between the CT genotype. BODE integral index, which is now used to assess not only the prognosis but also the severity of COPD and treatment efficacy, was also higher in COPD patients with type 2 diabetes mellitus than those with CT genotype. Carbohydrate and lipid metabolism in the comorbid course of disease differed between genotypes. Fasting glucose and total cholesterol were significantly higher than the TT genotype compared to the SS genotype, and LDL CL was higher than the TT genotype compared to the SS and CT genotype. The indicators of systemic inflammation and adipocytokines in the group of patients with comorbid pathology did not have a significant difference between the genotypes, although compared with the group of patients with COPD, there was a significant difference between the genotypes, especially for the SS genotype. Considering that endothelial dysfunction plays one of the leading links in pathogenesis of COPD and type 2 diabetes mellitus, association of MDR1 gene (C3435T) polymorphism with indicators of endothelial functional status has been studied. They have been found to be significantly worse in the group of patients with comorbid pathology compared to the group of COPD patients. At the same time, the level of nitrates / nitrites in patients with COPD with concomitant type 2 diabetes mellitus was significantly lower than the TT genotype compared to the SS genotype.

Conclusion

Therefore, the results of our study are indicative of the fact that there is no significant difference between the genotypes of the control group of healthy individuals and patients with COPD and comorbid type 2 diabetes mellitus. However, a certain association of this gene polymorphism with clinical findings has been established on the base of CAT test, certain indices of carbohydrate (fasting glucose) and lipid metabolism (total cholesterol and LDL cholesterol), endothelial functional state (nitrate / nitrite level) with T allele. Further investigation is required and possible use of the findings obtained to be implemented in personalized treatment in case of comorbidity of chronic obstructive pulmonary disease and type 2 diabetes mellitus, taking into account MDR1 (S3435T) gene polymorphism.

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