

ASSOCIATION OF THE ADRB2 GENE POLYMORPHIC VARIANT C79G (rs1072714) WITH THE COURSE OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE IN OBESE AND NON-OBESE PATIENTS

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Abstract:

Introduction: Attention has been paid to studying the role of the sympathetic nervous system and polymorphism of the β_2 -adrenoceptor genes in the development of chronic obstructive pulmonary disease (COPD) in recent years, but the findings of the studies contradict each other.

Objective: To establish an association between the ADRB2 gene polymorphic variant C79G (rs1072714) in obese and non-obese COPD patients.

Methods: The study involved 48 obese COPD patients and 52 nonobese COPD patients. The ADRB2 gene polymorphic variant C79G (rs1072714) was genotyped and assessed by the CAT test and the BODE index.

Results: It has been established that in obese COPD patients the CAT test was significantly higher in the genotype GG (24.25 ± 4.25) compared to those with obesity and the genotype CC and CG ($p < 0.05$). The BODE index was significantly ($p < 0.05$) lower in obese COPD patients. A strong positive correlation between BMI and FEV₁ ($r = 0.742$, $p = 0.014$) in nonobese COPD patients with GG genotype has been found.

Conclusion: According to the CAT test, the quality of life in obese COPD patients with GG genotype is worse. The BODE index in obese COPD patients with CC and CG genotypes was significantly lower than in those without obesity. A strong positive correlation between BMI and FEV₁ in COPD patients without obesity with GG genotype has been established.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a complex heterogeneous disease, the development of which is based on a genetic predisposition and environmental factors (GOLD, 2018).

The clinical and functional heterogeneity of patients with COPD in terms of the symptom severity, frequency and type of exacerbations, lung function, structural changes, local and systemic inflammation, as well as a response to a therapy have been proven (Barnes et al., 2009).

Twenty percent of smokers develop COPD primarily due to a genetic predisposition to the disease (GOLD, 2018). Today, the role of candidate genes in the development of COPD has been actively studied. In particular, in two meta-analyzes, the role of genes coding the synthesis of TNF α , TGF β ₁, glutathione-S-transferase P₁ and M₁, and superoxide dismutase 3 have been established (Hancock et al., 2010). Issac et al. (2014) studied the involvement of the gene polymorphism of the surfactant protein Drs2243639, IL-1 β rs16944 and IL-1RNrs2234663 in the pathology. The role of α_1 -antitrypsin deficiency in the development of pulmonary emphysema and COPD has been clearly identified (GOLD, 2018).

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Attention has been paid to studying the role of the sympathetic nervous system and the polymorphism of the β_2 -adrenoceptor genes in the development of chronic obstructive pulmonary disease in recent years, but the findings of the studies contradict each other (Thomsen et al., 2012; Randhawa et al., 2014). The aim of this study is to establish an association between the ADRB2 gene polymorphic variant C79G (rs1072714) in obese and non-obese COPD patients.

Methods

As a result of screening, 100 patients with COPD aged from 40 to 79 years (on average, 62.46 ± 2.21) were involved in the study. The inclusion criteria were: age more than 40 years; at least a 10 pack-year history of tobacco exposure; and Global Initiative for Obstructive Lung Disease (GOLD) stage criteria for COPD based on post-bronchodilator spirometry.

A questionnaire (the COPD Assessment Test (CAT)) was used to assess the symptoms.

Dyspnea level was measured by the modified Medical Research Council (mMRC) scale.

To assess exercise tolerance, a 6-minute walk test was conducted using the standard protocol (ATS statement guidelines, 2002).

To evaluate the severity of COPD, the BODE index was used. For the calculation of the BODE we used the model of Celli et al. (2004).

A bioelectrical impedance analysis was used to assess body composition. The measurements were carried out on a portable device VS-601 (TANITA, Japan). The body weight, BMI, muscle weight, fat weight percentage, visceral fat rate, metabolism in kcal, water % in the body, metabolic age, and % of trunk fat were determined.

To carry out molecular genetic studies, the genomic DNA was isolated from the peripheral blood. Genotyping of the ADRB2 gene polymorphic variants C79G was performed according to the protocol by Martinez et al. (1997).

To establish the association of the ADRB2 gene polymorphic variant C79G (rs1072714) within the course of the disease, COPD patients were divided into two groups according to their body mass index: those with obesity (48 people) and those without obesity - 52 individuals. Underweight COPD patients were excluded from the study.

The statistical processing of the findings was performed using the statistical software package Statistica 10.0 StatSoftInc.

A correlation analysis was carried out using the nonparametric Spearman's rank correlation coefficient.

Results and Discussion

An analysis of the CAT questionnaire findings, the dyspnea score scale, the BODE index, and a 6-minute walk test depending on the ADRB2 gene polymorphic variant C79G (rs1072714) (Table 1), was performed.

Values	Genotype	Obese COPD patients	Nonobese COPD patients
CAT-tests, scores	CC	13.93±1.61	17.42±1.89
	CG	19.72±1.21 p _{CC} <0.01	20.14±1.60
	GG	24.25±4.25 p _{CC} <0.05	22.70±2.97
dyspnea scale, scores	CC	2.47±0.17	2.76±0.14
	CG	2.66±0.14	2.86±0.13
	GG	2.75±0.48	2.80±0.25
BODE index, scores	CC	3.53±0.53	5.09±0.39*
	CG	4.28±0.37	5.71±0.46*
	GG	4.00±1.08	4.40±0.75
a 6 minute walk test	CC	346.33±25.94	301.67±21.55
	CG	323.10±18.62	280.71±17.87
	GG	287.50±39.45	264.12±14.53

Source: Authors

It has been established that in obese COPD patients the CAT test was significantly higher in those who are carriers of the CC and CG genotype ($p < 0.05$). When comparing obese COPD patients and those without obesity, there were no significant differences. There are no differences between the dyspnea scale (in scores) and a 6-minute walk test either.

The BODE index was lower ($p < 0.05$) in obese COPD patients (30.6% in the CC genotype and 25% in the CG genotype). There were no significant differences between the groups in the genotype GG.

Therefore, we have found that there were significant differences in obese COPD patients between genotypes and the highest total score of the CAT test was in the genotype GG.

The BODE integral index was significantly lower in obese COPD patients than in those without obesity who are carriers of the CC and CG genotype. In the genotype GG there were no significant differences between the group of obese and non-obese patients.

We carried out a correlation analysis between the values of bioelectrical impedance analysis and those of spirometry depending on the ADRB2 gene polymorphism (C79G) (Table 2, Table 3). There was a significant inverse proportional relationship between the level of visceral fat and the forced expiratory volume during the first second of the expiration (FEV_1) ($r = -0.570$, $p = 0.007$), FEV_6 ($r = -0.434$, $p = 0.05$), FEV_1 / FVC ($r = -0.486$, $p = 0.025$), FEV_1 / FEV_6 ($r = -0.485$, $p = 0.026$) in non-obese COPD patients with the CC genotype.

A negative correlation in this group of patients was also observed in pairs of % of body fat content - FEV_1 / FVC ($r = -0.496$, $p = 0.022$), % of body fat content - FEV_1 / FEV_6 ($r = -0.509$, $p = 0.018$). According to the genotype GG in non-obese COPD patients, a strong positive correlation between BMI and FEV_1 should be noted ($r = 0.742$, $p = 0.014$).

Obesity is associated with numerous lung problems, faster FEV_1 reduction, development of sleep apnea syndrome (Cecere et al., 2011; Vozoris et al., 2012; Melo et al., 2014). In COPD, obesity demonstrates itself by mixed effects, along with reduced exercise tolerance and lower quality of life, there is less severe airflow obstruction and reduced mortality (Franssen et al., 2008; Blum et al., 2011; Katz et al., 2016; Lambert et al., 2017).

The dependence of the onset and development of COPD on the ADRB2 gene polymorphism was studied as well (Nielson et al., 2017). Contradictory results were obtained. Some studies showed the dependence of the onset of the disease and the effect on the severity of the flow of the ADRB2 gene polymorphism (Konno et al., 2011). Other studies indicated a lack of the association (Mokry et al., 2008; Kim et al., 2009).

Various results have been obtained regarding the dependence of this polymorphism on obesity development (Zhang et al., 2014; Saliba et al., 2014; Aplalasy et al., 2015; Leonska-Duniec et al., 2016).

In our previous studies the association of the ADRB2 gene polymorphic variant C79G (rs1072714) with the development of obesity in COPD patients was shown (Gorovenko et al., 2014; Gorovenko et al., 2015).

In this work we studied the CAT test and the integral BODE index of COPD patients with and without obesity depending on the ADRB2 gene polymorphic variant C79G (rs1072714).

According to GOLD recommendations, the CAT test is used to assess the COPD effect on patients' quality of life (GOLD, 2018). This value was studied in different populations of patients depending on age, sex, status of smoking, in persons with non-diagnosed COPD and COPD severity (Gupta et al., 2016). A deterioration in the health status with an increase in the severity of obstruction and the frequency of exacerbation was established (Koniska et al., 2015; Lopez-Campos et al., 2015; Garcia-Sidro et al., 2015; Srivastava et al., 2017).

It has been found that in obese COPD patients the CAT test had differences in the genotypes CC, CG and GG. In those who are carriers of the GG genotype this value was the highest one.

The obtained data may be indicative of the fact that in obese COPD patients with the GG genotype a subjective evaluation of the disease is worse.

As many studies (Celli et al., 2008; Cote et al., 2009; Corlateanu et al., 2016) and recommendations of GOLD indicate (GOLD, 2018), one cannot estimate the severity and prognosis of COPD based on one value. The BODE integral index proposed by Celli et al. (2004) as a prognostic index has recently been

used to assess the severity of the disease and the effectiveness of the drug and pulmonary rehabilitation programs (Ong et al., 2005; Kavoura et al., 2016; Nakato et al., 2016).

According to our study, the BODE index had a significant difference between the groups of patients with and without obesity in CC and CG genotypes and was lower in the group of obese patients. In the homozygous GG genotype, the severity of the disease (according to the BODE index) did not depend on the presence of the concomitant obesity.

Some studies investigated the relationship between the spirometry parameters and BMI (van den Borst et al., 2011; Abston et al., 2017). Underweight COPD patients showed worse spirometry values (Eriksson et al., 2016).

Overweight and obese COPD patients had less severe airflow obstruction than underweight patients. A low BMI in COPD patients is known to be a mortality predictor (Landbo et al., 1999; Hallin et al., 2007). Therefore, it is important to study the structure of the body, namely the muscle mass in patients with COPD.

This work studied the correlations between the spirometry values and those of bioelectrical impedance analysis in COPD patients without and with obesity depending on the ADRB2 gene polymorphic variant C79G (rs1072714).

It was determined that in non-obese COPD patients there was a strong positive correlation between BMI and FEV₁ in the GG genotype. This is important in order to manage this contingent of patients in the future. Such patients should monitor the spirometry and bioelectrical impedance analysis values, since further reduction of BMI may affect the life expectancy for these patients.

Conclusion

It has been established that the impact of COPD on the quality of life of patients according to the CAT test is more pronounced in obese COPD patients with the GG genotype. The BODE index in obese COPD patients with the CC and CG genotypes was significantly lower than in those without obesity. In patients with the homozygous genotype GG, the more severe course of the disease did not depend on the presence of obesity. A strong positive correlation between the BMI and the FEV₁ in non-obese COPD patients with the GG genotype was determined.

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