ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Body Mass Index in Patients with Bronchial Asthma with Regard to Gln27Glu Polymorphism β_2-Adrenergic Receptor Gene.

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ABSTRACT

Bronchial asthma (BA) and obesity due to their high prevalence and medical and social significance belong to global problems of healthcare. Obesity effect on asthma development includes the following mechanisms: impact on respiratory function, inflammation and common genetic factors. The aim of our research was to study the association between BMI and Gln27Glu polymorphism in the $ADRB_2$ gene in BA patients. Patients with bronchial asthma were divided into 3 groups depending on their BMI: Group I – 110 patients with normal body mass; group II – 26 overweight patients, group III – 59 obese patients. Gln27Glu polymorphism in the $ADRB_2$ gene was detected using polymerase chain reaction. Statistical analysis was performed using SPSS–21 program. P-value <0.05 was considered significant. Obtained results showed that obesity occurred more often in Glu27Glu genotype carriers, while normal body mass was more characteristic of Gln27Gln genotype carriers (p = 0.001). Distribution of BMI with regard to Gln27Glu polymorphism in the $ADRB_2$ gene in BA patients did not depend on gender (p=0.1). Thus, BA patients with Glu27Glu genotype of the $ADRB_2$ gene had obesity significantly more often.

Keywords: bronchial asthma, obesity, β_2-adrenoceptor, Gln27Glu polymorphism.

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ISSN: 0975-8585

INTRODUCTION

Bronchial asthma (BA) and obesity due to their high prevalence and medical and social significance belong to global problems of healthcare. Analysis of population-based studies of body mass index (BMI) in the world [6, 20] allowed not only tracing the increase of number of obese people and asserting "obesity epidemic", but also creating on this basis a ranking of countries with the highest obesity prevalence, among which Mexico (32.8%) and the USA (31.8 %) ranked first [7]. BA is of equal significance as concerns its prevalence. Epidemiological study of asthma revealed a tendency to rapid increase in the disease incidence. According to the Bulletin of the World Health Organization [3], the countries with the highest prevalence of asthma are Great Britain – 18.4% and New Zealand – 15.1%.

BA morbidity level has lately increased among obese adult population, especially among women. Obesity is a factor that contributes to asthma development and worsens disease control, which is confirmed by changes in quality of life, limitations in daily activities, severity of apnea and wheezing, frequency of rescue medication use, increase in unscheduled doctor visits, ambulance calls and hospitalizations for exacerbations [7, 21, 22].

Obesity increases the risk of asthma and is a risk factor for persistence and asthma symptoms severity in children and adults [4, 5, 11]. Obesity effect on asthma includes the following mechanisms: respiratory function changes, inflammation and common genetic factors [2, 18, 19], in particular pleiotropic effect that is typical for polymorphisms in the β_2-adrenergic receptor ($ADRB_2$) genes and glucocorticosteroid (GC) receptor genes, which are located on chromosome 5q23-34 and are responsible for airways tone, sympathetic nervous system activity, and modulation of inflammation both in BA and obesity [1, 9, 13].

$ADRB_2$ is known to be one of the main lipolytic receptors in human adipose cells; genetic variation of the receptor gene is associated with obesity development, energy expenditure and lipolytic function of adipose tissue [9, 10, 15, 17].

Thus, the **aim of our research** was to study the association between BMI and Gln27Glu polymorphism in the $ADRB_2$ gene in BA patients.

MATERIALS AND METHODS

We examined 195 patients with BA – 129 men and 66 women – aged 21-71, who were undergoing hospital treatment at the pulmonary department at MI of Sumy Regional Council “Sumy Regional Clinical Hospital”.

Patients with bronchial asthma were divided into 3 groups depending on their BMI. Group I comprised 110 patients with normal body mass; group II – 26 overweight patients, group III – 59 obese patients. BA was diagnosed in accordance with the GINA guidelines (2016) and the Decrees of the Ministry of Health of Ukraine №128 issued on 19-Mar-2007 and № 868 issued on 08-Oct-2013. BMI was assessed according to WHO criteria (1999).

The control group consisted of 95 apparently healthy individuals with no allergies and no history of atopic diseases.

Gln27Glu (rs1042714) polymorphism in the $ADRB_2$ gene was detected using polymerase chain reaction with subsequent analysis of restriction fragment length polymorphism by means of separation with agarose gel electrophoresis. Statistical analysis was performed using SPSS–21 program. Significance of differences between the control group and BA patients was estimated by Pearson's chi-squared test (the value of $p<0.05$ was considered statistically significant). The data were statistically processed using nonparametric statistical techniques, because Gaussian distribution of BMI parameters was far from normal. BMI was expressed through the median and interquartile range (25-th and 75-th percentiles). Obtained values of BMI were compared by means of rank analysis of variance (ANOVA) by Kruskal-Wallis. With this method we checked the null hypothesis of no difference among groups. With $p>0.05$, the null hypothesis of no difference in median values of groups was confirmed, that is groups did not differ. With $p<0.05$, the null hypothesis was not confirmed and, respectively, the alternative hypothesis was accepted stating that there were differences in

median values of groups. In this case, we performed pair-wise comparison of groups using Mann-Whitney nonparametric test. To evaluate the influence of polymorphism genotypes on obesity risk in BA patients, the odds ratio (OR) and 95% confidence interval (CI) were calculated.

RESULTS

Genotype distribution of Gln27Glu polymorphism in the $ADRB_2$ gene with regard to BMI in BA patients and the control group is presented in Table 1 and Table 2. Obtained results showed that obesity occurred more often in the BA patients who were Glu27Glu genotype carriers (p = 0.001 by Pearson's chi-squared test), while in the control group there was no significant difference, that is, genotypes had equal frequency for different BMI values (p = 0.9 by Pearson's chi-squared test).

Table 1: Genotypes distribution of Gln27Glu polymorphism in the β_2-adrenoceptor gene in dependence on body mass index in the control group

	Control group			
BMI / Genotypes	Normal body mass		Overweight	
	n	%	n	%
Gln27Gln	28	75.7	9	24.3
Gln27Glu	29	76.3	9	23.7
Glu27Glu	16	80.0	4	20.0
	$\chi^2 = 3.4$; p = 0.9			

Table 2: Genotypes distribution of Gln27Glu polymorphism in the β2-adrenoceptor gene in dependence on body mass index in the patients with bronchial asthma

	BA patients					
BMI / Genotypes	Normal body mass		Overweight		Obesity	
	n	%	n	%	n	%
Gln27Gln	74	71.2	18	17.3	12	11.5
Gln27Glu	34	49.3	4	5.8	31	44.9
Glu27Glu	2	9.1	4	18.2	16	72.7
	$\chi^2 = 22.8$; p = 0.001					

Performed analysis of association between BMI and Gln27Glu polymorphism in the $ADRB_2$ gene in BA patients is presented in Table 3.

Table 3: The median (interquartile range) of body mass index in patients with bronchial asthma with regard to Gln27Glu polymorphism in the ADRB2 gene

Values / Genotypes	BMI, kg/m^2
Gln27Gln (n=110)	24.8 (23.8 – 25.8)
Gln27Glu (n=26)	28.9 (27.2 – 30.7)
Glu27Glu (n=59)	32.6 (30.9 – 34.3)

The results of analysis demonstrated a statistically significant difference in BMI with regard to Gln27Glu polymorphism in the $ADRB_2$ gene (p=0.001 by Kruskal-Wallis).

The next step included pair-wise comparison of groups using Mann-Whitney test. As comparing BMI values in carriers of Gln27Gln vs. Gln27Glu genotypes, as well as in carriers of Gln27Glu vs. Glu27Glu

genotypes, a statistically significant difference was established ($p_1 < 0.001$ and $p_2 < 0.001$). That is, the patients with Glu27Glu genotype had higher BMI values than the patients with Gln27Gln and Gln27Glu genotypes.

Analysis of BMI values with regard to the genotype of the Gln27Glu polymorphism in the $ADRB_2$ gene in patients of different sex demonstrated that in men there was a statistically significant difference in BMI with regard to Gln27Gln, Gln27Glu and Glu27Glu genotypes in the $ADRB_2$ gene (p=0.001 by Kruskal-Wallis) (Fig.2). Thus, higher values of BMI were observed in men with BA and Glu27Glu genotype of the $ADRB_2$ gene as compared with male carriers of Gln27Gln and Gln27Glu genotypes (p_1=0.001 and p_2=0.005 by Mann-Whitney); though, there was no significant difference in BMI between male carriers of Gln27Glu vs Glu27Glu genotypes (p_3=0.1 by Mann-Whitney). In women there also was a statistically significant difference in BMI (p=0.001 by Kruskal-Wallis) (Fig. 3). Female patients with BA and Glu27Glu genotype of the $ADRB_2$ gene had higher BMI values as compared with those having Gln27Gln and Gln27Glu genotypes of Gln27Glu polymorphism in the $ADRB_2$ gene (p=0.001 by Mann-Whitney).

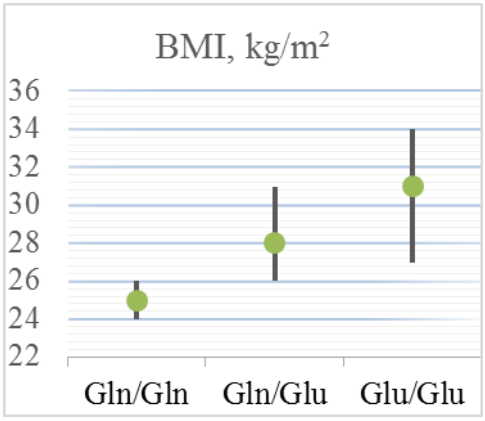

Figure 2. The median (interquartile range) of BMI values in men

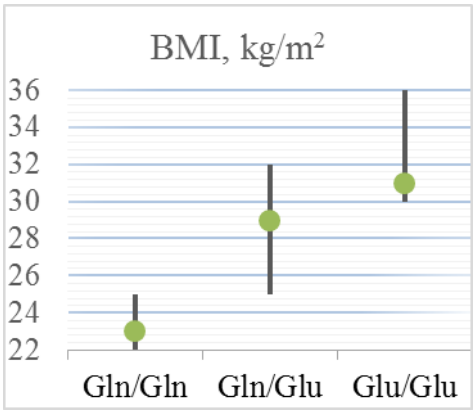

Figure 3. The median (interquartile range) of BMI values in women

DISCUSSION

According to the data of epidemiological studies performed among adults with BA, obesity was found to precede bronchial asthma and double asthma risk in men and women (OR = 1.92, CI − 95% 1.43 − 2.59, p <0.0001) [2].

Meta-analysis of 18 studies demonstrated association of Gln27Glu polymorphism with obesity risk in heterozygous model (Gln/Glu vs Gln/Gln: OR = 1.16; CI − 95% 1.04 – 1.30, p = 0.009) and dominant model (Gln/Glu + Glu/Glu vs Gln/Gln: OR = 1.2; CI − 95% 1.00 – 1.44, p = 0.04) [23]. Ishiyama-Shigemoto S. et al (1999) in their study also stated that frequency of Glu27Glu genotype was two times higher in obese patients as compared with the control group (p= 0.001) [9]. In our study we documented higher frequency of Glu27Glu genotype in obese patients as compared with Gln27Gln and Gln27Glu genotypes (p = 0.001). These studies show that Gln27Glu polymorphism in the $ADRB_2$ gene is involved into obesity pathogenesis.

Leite N. et al. (2015) proved that Glu27 allele was observed more often in overweight patients with BA as compared with those having normal body mass (p = 0.03) [14]. Still, other studies demonstrated association of obesity with Gln/Gln genotype of Gln27Glu polymorphism in the $ADRB_2$ gene. Thus, Maha H. et al. (2008) established that the frequency of Gln/Gln homozygotes was higher among obese patients, who had higher concentration of triglycerides, leptin and insulin, as compared with Gln/Glu heterozygotes and the minor allele (Glu/Glu) homozygotes [15]. Unlike the above-mentioned study, B. Kortner and A. Wolf when determining the frequency of Gln27Glu polymorphism in the $ADRB_2$ gene in patients with morbid obesity vs the control group showed that the frequency of Glu/Glu genotype was almost identical in both groups (0.41 and 0.43, respectively; p = 0.68). The researchers found no evidence of association between Gln27Glu polymorphism in the $ADRB_2$ gene and development of morbid obesity [12].

Large V. et al. (1997) documented an association between Gln27Glu polymorphism in the $ADRB_2$ gene and gender features, that is, female carriers of Glu27Glu genotype had 2.09 times higher risk of obesity (OR = 2.09, CI – 95% 1.17 – 3.74, p=0.01) as compared with men [13]. Hellström L. and Large V. (2008) in their study found positive correlation between obesity and Gln27Glu polymorphism in the $ADRB_2$ gene in women, while in men they observed negative correlation (p = 0.013) [8]. These data suggest that genetic factors have different effects on obesity development in men and women.

Unlike the previous researchers, Mori Y. and Kim-Motoyama H. (2009), when studying the influence of Gln27Glu polymorphism in the $ADRB_2$ gene on obesity development and subcutaneous fat distribution, demonstrated much higher frequency of Glu/Glu genotype in obese men as compared to obese women (p = 0.04) [17]. Our results concerning distribution of genotypes of Gln27Glu polymorphism in the $ADRB_2$ gene with regard to BMI and gender in BA patients showed no significant differences.

Thus, these study results show that obesity was observed more frequently in Glu27Glu genotype carriers, while normal body mass – in the carriers of Gln27Gln genotype of Gln27Glu polymorphism in the $ADRB_2$ gene in BA patients, which is congruent with the data of foreign researches.

CONCLUSIONS

- BA patients with Glu27Glu genotype of the $ADRB_2$ gene had obesity significantly more often as compared with Gln27Gln and Gln27Glu genotype carriers.
- Distribution of genotypes of Gln27Glu polymorphism in the $ADRB_2$ gene with regard to BMI and gender in BA patients showed no significant differences.

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