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ASSOCIATION BETWEEN GLN27GLU POLYMORPHISM IN THE B2 ADRENERGIC RECEPTOR GENE AND OBESITY RISK IN PATIENTS WITH EARLY-ONSET AND LATE-ONSET BRONCHIAL ASTHMA

Vladyslava Kachkovska.

Associate Professor, Department of Internal Medicine with Respiratory Medicine Center, Sumy State University, 116, Kharkivska str., Sumy, Ukraine.

Abstract.

Aim: The objective of our study was to investigate the association between the Gln27Glu polymorphism in the β2-AR gene and body mass index (BMI) in patients with bronchial asthma (BA) with regard to the age of onset.

Materials and Methods: Study included 553 patients with BA and 95 apparently healthy individuals with no individual and family history of asthma symptoms. All of them had previously signed an informed consent form for study participation. The patients were divided into 2 clinical groups depending on the age of BA onset. Group I included 282 patients with late-onset asthma (late-onset asthma phenotype), and Group II included 271 patients with early-onset asthma (early-onset asthma phenotype). There was no significant difference in gender, age, severity, or control level between the groups (p > 0.05). BA diagnosis and BA severity were determined according to the GINA recommendations-2016 and its later version. Obesity was diagnosed in accordance with the Order of the Ministry of Health of Ukraine № 574 dated 05.08.2009 and the WHO recommendations (1999), the European Association for the Study of Obesity (EASO, 2016). The Gln27Glu polymorphism in the β2-AR gene (rs1042714) was determined using polymerase chain reaction-restriction fragment length polymorphism analysis. The obtained results were statistically analyzed using SPSS–17 program.

Results: No significant difference was established in the distribution of alleles and genotypes for the Gln27Glu polymorphism in the β2-AR gene and obesity risk in patients with early-onset bronchial asthma in any model of inheritance. Obesity relative risk estimation showed a statistically significant correlation related to the dominant (p = 0.03) and additive (p = 0.04) models of inheritance. The risk of obesity in minor allele carriers (Glu/Glu+Gln/Glu) was 1.75 times higher than that in the major allele homozygotes (p = 0.03). No association was observed between the Gln27Glu polymorphism in the β2-AR gene and obesity risk in patients with early-onset bronchial asthma in any model of inheritance. Obesity relative risk estimation in late-onset BA patients showed a statistically significant correlation related to the dominant (p = 0.03) and additive (p = 0.001) models of inheritance. The minor allele carriers (Gln/Glu and Gln/Glu genotypes) with late-onset BA had a 1.95 times higher risk of obesity in the dominant model and 1.65 times higher risk of obesity in the additive model vs. the major allele homozygotes.

Conclusions: The obtained data indicated that the minor allele carriers of the Gln27Glu polymorphism in the β2-AR gene (both homozygotes and heterozygotes) with late-onset BA had a higher risk of obesity.

Key words. Bronchial asthma, onset, obesity, Gln27Glu polymorphism in the β2-adrenocceptor gene.

Introduction.

Obesity-associated bronchial asthma (BA) is known to be a specific clinical phenotype characterized by a more severe course and a lower level of control due to insufficient response to background therapy. BA and obesity are recognized as typical multifactorial diseases that occur in individuals with a particular genotype under the influence of triggering environmental factors [1,2]. The results of genetic studies on the comorbidity of these diseases revealed shared genetic factors that were associated with pleiotropic effects of the genes of the β2-adrenoceptor (AR), glucocorticoid receptors, and leptin receptors, TNF-α, and others. Specific human genomic regions associated with both asthma and obesity were identified [1,3]. In particular, polymorphic variants of the β2-AR gene were associated with BA [4,5] and obesity [6-9]. Therefore, single nucleotide polymorphisms in the β2-AR gene require further study in the context of BA-obesity phenotype, since bronchial hyperreactivity and poor response to bronchodilating treatment are related to the same defect, which stimulates lipid mobilization through adipocyte lipolysis. The study by Hallstrand et al. on the shared genetic origin of asthma and obesity showed a strong association between asthma and obesity and confirmed their genetic pleiotropy by revealing that 8% of genetic factors were shared by BA and obesity.

The results of large-scale genome-wide association studies proved the genetic contribution to the development of BA and related diseases (including obesity). They demonstrated both shared and distinct genetic components [3,10], which allows for a better understanding of the mechanisms of the phenotypic features.

For asthma as a polygenic disease, the age of onset is of diagnostic and prognostic value [11,12]. A significant difference was observed among genetic factors depending on the age of BA onset and specific genetic variants of early-onset and late-onset BA risk were demonstrated, which can partially explain the differences in their pathogenesis. Studies of genomic associations with the age of asthma onset, as a key factor in identifying risk variants for a particular disease phenotype [13], can help understand the differences in the pathogenesis, clinical course, and treatment approaches between early-onset and late-onset asthma. The heterogeneity of the data related to the role of β2-AR gene polymorphisms was due to different study objectives, designs, and populations. These contradictory results substantiate the advisability of further study on molecular and genetic mechanisms of BA—obesity association pathogenesis and pleiotropic effects of β2-AR genes in order to develop options for predicting these diseases [14-16].

The objective of our study was to investigate the association between the Gln27Glu polymorphism in the β2-AR gene and
body mass index (BMI) in patients with BA with regard to the age of onset.

Materials and Methods.

553 patients with bronchial asthma were examined. All of them had previously signed an informed consent form. The control group consisted of 95 apparently healthy individuals with no individual and family history of asthma symptoms; with no history of smoking, allergies or atopy, hypersensitivity to aspirin and nonsteroidal anti-inflammatory drugs, acute or chronic somatic diseases in the acute stage within 3 months prior to the enrollment. Among the studied patients, there were 360 women (65.1%) and 193 men (34.9%); the control group consisted of 45 men (47.4%) and 50 women (52.6%). The patients were divided into 2 clinical groups depending on the age of BA onset. Group I included 282 patients with late-onset asthma (late-onset asthma phenotype), and Group II included 271 patients with early-onset asthma (early-onset asthma phenotype). There was no significant difference in gender, age, severity, or control level between the groups (р > 0.05). BA diagnosis and BA severity were determined according to the GINA recommendations-2016 and its later versions [17]. Obesity was diagnosed in accordance with the Order of the Ministry of Health of Ukraine № 574 dated 05.08.2009, "On approval of the protocols for medical care for patients with endocrine diseases" and the WHO recommendations (1999), the European Association for the Study of Obesity (EASO, 2016). BMI of 18 kg/m² to 24.9 kg/m² was regarded as normal body weight (healthy weight), 25 kg/m² to 29.9 kg/m² – as overweight, BMI of higher than 30 kg/m² – as obesity. The study was approved by the Bioethics Committee of the Academic and Research Medical Institute of Sumy State University. The Gln27Glu polymorphism in the β2-AR gene (rs1042714) was determined using polymerase chain reaction-restriction fragment length polymorphism analysis. The obtained results were statistically analyzed using SPSS–17 program. The distribution of genotypes in the studied groups was compared using Pearson's chi-squared test. In order to determine the risk of BA and obesity, the odds ratio (OR) and 95% confidence interval (CI) for dominant, recessive, superdominant, and additive inheritance models were calculated. The relevance of the obtained results was assessed with Akaike's information criterion. All tests were two-sided; the p-value of <0.05 was considered statistically significant.

Results.

Among the subjects with BA, 195 (35.2%) were obese, 206 (37.3%) were overweight, and only 152 (27.5%) had a healthy weight. Due to the fact that the association was proved between certain polymorphic variants in the β2-AR gene, including Gln27Glu polymorphism, and the development of obesity [2,18], we analyzed the distribution of genotypes and alleles for this polymorphism in the examined BA patients with regard to BMI (Table 1) and investigated the association with obesity risk (Table 2).

The results of the statistical analysis of obesity risk with regard to the Gln27Glu polymorphism in the β2-AR gene are presented in Table 2.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Body mass index, n = 553</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy weight, n = 152</td>
</tr>
<tr>
<td></td>
<td>n %</td>
</tr>
<tr>
<td>Gln/Gln</td>
<td>81 53.3</td>
</tr>
<tr>
<td>Gln/Glu</td>
<td>64 42.1</td>
</tr>
<tr>
<td>Glu/Glu</td>
<td>7 4.6</td>
</tr>
<tr>
<td></td>
<td>χ² = 7.77; p = 0.1</td>
</tr>
<tr>
<td>Gln-allele</td>
<td>74.3</td>
</tr>
<tr>
<td>Glu-allele</td>
<td>25.7</td>
</tr>
</tbody>
</table>

No significant difference was established in the distribution of alleles and genotypes for the Gln27Glu polymorphism in the β2-adrenergic receptor gene depending on BMI (p = 0.1). Obesity relative risk estimation showed a statistically significant correlation related to the dominant (p = 0.03) and additive (p = 0.04) models of inheritance. The risk of obesity in minor allele carriers (Glu/Glu+Gln/Glu) was 1.75 times higher than that in the major allele homozygotes (p = 0.03). The obtained data indicated that the minor allele carriers (both homozygotes and heterozygotes) had a higher risk of obesity.

The analysis of genotype distribution of the Gln27Glu polymorphism in the β2-adrenergic receptor gene in BA patients with regard to the age of onset is given in Table 3.

According to the obtained results, the minor allele homozygotes were observed almost twice as often among patients with early-onset BA and obesity vs. patients with healthy weight or overweight (p = 0.019). Accordingly, allele frequency analysis demonstrated the highest frequency of the Glu-allele in obese patients with BA. In patients with late-onset BA, homoyzogous carriers of the minor allele were more often reported among patients with overweight and obesity vs. patients with healthy weight (p = 0.03).

Taking into account the observed statistically significant difference in the distribution of genotypes for the Gln27Glu polymorphism in the β2-AR gene in patients with early-onset and late-onset BA depending on BMI, we analyzed the risk of obesity in four models of inheritance (Table 4).

No association was observed between the Gln27Glu polymorphism in the β2-AR gene and obesity risk in patients with early-onset bronchial asthma in any model of inheritance. Obesity relative risk estimation in late-onset BA patients showed a statistically significant correlation related to the dominant (p = 0.03) and additive (p = 0.001) models of inheritance. The minor allele carriers (Glu/Glu and Gln/Glu genotypes) with late-onset BA had a 1.95 times higher risk of obesity in the dominant model.
Table 3. Genotype and allele distribution of Gln27Glu polymorphism in the β2-adrenoceptor gene depending on the body mass index in patients with bronchial asthma.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Healthy weight, n = 84</th>
<th>Overweight, n = 87</th>
<th>Obesity, n = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Gln/Gln</td>
<td>54</td>
<td>64.3</td>
<td>70</td>
</tr>
<tr>
<td>Gln/Glu</td>
<td>26</td>
<td>31.0</td>
<td>13</td>
</tr>
<tr>
<td>Glu/Glu</td>
<td>4</td>
<td>4.7</td>
<td>4</td>
</tr>
</tbody>
</table>

$\chi^2 = 11.83; p = 0.019$

<table>
<thead>
<tr>
<th>Allele</th>
<th>Healthy weight, n</th>
<th>Overweight, n</th>
<th>Obesity, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gln</td>
<td>79.8</td>
<td>87.9</td>
<td>75.0</td>
</tr>
<tr>
<td>Glu</td>
<td>20.2</td>
<td>12.1</td>
<td>25.0</td>
</tr>
</tbody>
</table>

Table 4. Obesity risk in BA patients with regard to the Gln27Glu polymorphism in the β2-adrenoceptor gene.

<table>
<thead>
<tr>
<th>Model</th>
<th>$P_{obs}$</th>
<th>$OR_{obs}$ (95% CI)</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant</td>
<td>0.13</td>
<td>1.57 (0.87–2.84)</td>
<td>16.87</td>
</tr>
<tr>
<td>Recessive</td>
<td>0.65</td>
<td>1.29 (0.43–4.06)</td>
<td>18.94</td>
</tr>
<tr>
<td>Super-dominant</td>
<td>0.18</td>
<td>1.52 (0.82–2.86)</td>
<td>16.77</td>
</tr>
<tr>
<td>Additive</td>
<td>0.18</td>
<td>1.37 (0.87–2.18)</td>
<td>17.31</td>
</tr>
</tbody>
</table>

and 1.65 times higher risk of obesity in the additive model vs. the major allele homozygotes. The obtained data indicated that the minor allele carriers (both homozygotes and heterozygotes) with late-onset BA had a higher risk of obesity.

**Discussion.**

The association between the Gln27Glu polymorphism in the β2-AR gene and the risk of asthma, which was proven in numerous studies, still relates to contradictory and sometimes opposite results in other studies [19-21]. Some studies, in particular on pediatric asthma, also demonstrated that the Gln27Glu polymorphism in the β2-AR gene was not associated with a higher risk of asthma in different ethnic groups within the general population [19,21,22]. Contradictory results were obtained regarding the role of the Gln27Glu polymorphism in the β2-AR gene in obesity development; the study showed that rs1042714 could be a significant risk factor for obesity in Asians, Pacific Islanders, and American Indians, but not in Europeans [23]. Another meta-analysis demonstrated that the Gln27Glu polymorphism in the β2-AR gene was associated with an increased risk of obesity in Glu/Glu heterozygotes vs. Gln/Gln (OR 1.16; 95% CI 1.04–1.30, $p = 0.009$) and in the carriers of Gln/Glu and Glu/Glu vs. Gln/Gln (OR 1.2; 95% CI 1.00–1.44, $p = 0.04$) [2]. Therefore, the Gln27Glu polymorphism is associated with a 1.2-fold higher risk of obesity in the carriers of Gln/Glu+Glu/Glu genotypes compared to Gln/Gln homozygotes, but the degree of the correlation between the studied polymorphic variants of the β2-AR gene and obesity varied in different populations. As opposed to the results of Jalba M.S., a meta-analysis by Zhang N. showed that the Gln27Glu polymorphism in the β2-AR gene is associated with obesity [2]. This may be due to genetic variability in the 27th codon and the interaction of genes and the environment since the mechanism of association between Glu27 and obesity is currently unknown. The results of this meta-analysis confirm that the predisposition to obesity has a statistically significant association with the Gln27Glu polymorphism in the β2-AR gene.

This is inconsistent with the previous results obtained by Echwald S.M. and Oberkofler N. [24] and others, who could not establish any association between this gene polymorphism and the risk of obesity. Large V. et al. found that the Gln27Glu polymorphism was associated with a relative risk of developing obesity, and Glu27 homozygotes had an average fat mass excess of 20 kg as compared to controls [18]. These data suggest that genetic variability in the β2-AR gene may play an important role in the development of obesity, energy expenditure, and lipolytic function of β2-AR in adipose tissue, at least in women. Ehrenborg E. also found that individuals with the Glu27 and/or Gly16 alleles had a significantly higher BMI [25]. In the Ukrainian population, there is only one study on the correlation between Gln27Glu in the β2-AR gene and body weight in patients with coronary heart disease, which showed that the Glu/Glu minor allele homozygotes had increased BMI, as well as
as increased insulin levels, insulin resistance, and triglyceride level.

In our previous study on a smaller sample of BA patients (n = 195), we established a correlation between BMI and Gln/Glu, Gln/Glu, and Glu/Glu genotypes for the Gln27Glu polymorphism in the β₂-AR gene, i. e. 24.5 ± 0.45; 29 ± 0.87, and 33.1 ± 0.89 kg/m², respectively (p<0.01) [27]. In our study involving 553 BA patients, we found no significant difference in the distribution of genotypes for the Gln27Glu polymorphism in the β₂-AR gene depending on BMI (χ² = 7.77; p = 0.1). Along with this, we observed a 1.75-fold (p = 0.03) increase in obesity risk for the dominant model and a 1.51-fold (p = 0.04) increase – for the additive model of inheritance.

We established a significant difference in the distribution of genotypes for the Gln27Glu polymorphism in the β₂-AR gene depending on the age of BA onset (χ² = 41.24; p = 0.001) and an increased risk of developing late-onset BA for the additive (p = 0.001), dominant (p = 0.001), and super-dominant (p = 0.001) models. The risk of developing late-onset asthma in the minor allele carriers (Gln/Glu and Glu/Glu genotypes) had a higher risk of late-onset BA. The risk of early-onset BA, unlike late-onset BA did not correlate with the Gln27Glu polymorphism in the β₂-AR gene in any model of inheritance.

This became the basis for the analysis of obesity risks in patients with asthma, depending on the age of onset. The analysis showed an increased relative risk of obesity in the minor allele carriers (Glu/Glu and Glu/Glu genotypes) with late-onset asthma in the dominant (by 2.62 times) and additive (by 2.0 times) inheritance models vs. the major allele homozygotes. At the same time, no association was observed between the Gln27Glu polymorphism in the β₂-AR gene and obesity risk in patients with early-onset bronchial asthma in any model of inheritance.

The results we obtained in the previous study indicating the increased risk of late-onset asthma in minor allele carriers (heterozygotes and the minor allele homozygotes) and the results of the current study indicating the increased risk of obesity in Glu-allele carriers suggest a shared genetic origin of late-onset BA and obesity. The studied polymorphism presents pleiotropic features with late-onset asthma and obesity in contrast to early-onset asthma. It may become a target for the prevention and treatment of asthma and obesity in the future. The observed association in BA–obesity comorbidity in the case of late-onset BA with Gln27Glu polymorphism in the β₂-AR gene presents evidence of pleiotropy and requires further detailed study.

Conclusion.

1. No significant difference was established in the distribution of the genotypes for the Gln27Glu polymorphism in the β₂-AR gene depending on BMI (p = 0.1).

2. We observed a 1.75-fold (p = 0.03) increase in obesity risk for the dominant model and a 1.51-fold (p = 0.04) increase – for the additive model of inheritance.

3. The minor allele homozygotes were observed almost twice as often among patients with early-onset BA and obesity vs. patients with healthy weight or overweight (p = 0.019) and 2.6 and 4.2 times more often among patients with late-onset BA + overweight and late-onset BA + obesity, respectively (p = 0.03), vs. patients with healthy weight.

4. No association was observed between the Gln27Glu polymorphism in the β₂-AR gene and obesity risk in patients with early-onset bronchial asthma in any model of inheritance, while the minor allele carriers (Gln/Glu and Glu/Glu genotypes) with late-onset BA had 1.95 times higher risk of obesity in the dominant model and 1.65 times higher risk of obesity in the additive model vs. the major allele homozygotes.

Conflict of interest.

The authors declare no conflict of interest. The study was funded at its own expense. The study was approved by the Bioethics Committee of Medical Institute of Sumy State University.

REFERENCES


17. GINA 2016 Guidelines.