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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman (Кириллица)**, для текста на грузинском языке следует использовать **AcadNusx**. Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и http://www.nlm.nih.gov/bsd/uniform_requirements.html В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректур авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf

In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned
Requirements are not Assigned to be Reviewed.**

ავტორთა საქურაღებოლ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დაიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx**. შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალებების შედეგების ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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ASSOCIATION BETWEEN GLN27GLU POLYMORPHISM IN THE β_2 ADRENERGIC RECEPTOR GENE AND OBESITY RISK IN PATIENTS WITH EARLY-ONSET AND LATE-ONSET BRONCHIAL ASTHMA

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Abstract.

Aim: The objective of our study was to investigate the association between the Gln27Glu polymorphism in the β_2 -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 β_2 -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 β_2 -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 ($p = 0.03$). No association was observed between the Gln27Glu polymorphism in the β_2 -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 Glu/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 β_2 -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 β_2 -adrenoceptor 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 β_2 -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 β_2 -AR gene were associated with BA [4,5] and obesity [6-9]. Therefore, single nucleotide polymorphisms in the β_2 -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 β_2 -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 β_2 -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 β_2 -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 ($p > 0.05$). 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 β_2 -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 β_2 -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 β_2 -AP gene are presented in Table. 2.

Table 1. Genotype and allele distribution of Gln27Glu polymorphism in the β_2 -adrenoceptor gene depending on the body mass index in patients with bronchial asthma.

Genotype	Body mass index, n = 553					
	Healthy weight, n = 152		Overweight, n = 206		Obesity, n = 195	
	n	%	n	%	n	%
Gln/Gln	81	53.3	103	50.0	108	55.4
Gln/Glu	64	42.1	77	37.4	68	34.9
Glu/Glu	7	4.6	26	12.6	19	9.7
$\chi^2 = 7.77; p = 0.1$						
Gln-allele	74.3		68.7		72.8	
Glu-allele	25.7		31.3		27.2	

Table 2. Analysis of the association between Gln27Glu polymorphism in the β_2 -adrenergic receptor gene and obesity.

Model	P _{obs}	OR _{obs} (95% CI)	AIC
Dominant	0.03	1.75 (1.05–2.95)	17.7
Recessive	0.33	1.6 (0.65–4.52)	21.28
Super-dominant	0.1	1.58 (0.92–2.78)	19.5
Additive	0.04	1.51 (1.02–2.3)	18.03

No significant difference was established in the distribution of alleles and genotypes for the Gln27Glu polymorphism in the β_2 -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 β_2 -adrenoceptor 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, homozygous 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 β_2 -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 β_2 -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 Glu/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 β_2 -adrenoceptor gene depending on the body mass index in patients with bronchial asthma.

Early onset						
Genotype	Healthy weight, n = 84		Overweight, n = 87		Obesity, n = 100	
	n	%	n	%	n	%
Gln/Gln	54	64.3	70	80.5	58	58.0
Gln/Glu	26	31.0	13	14.9	34	34.0
Glu/Glu	4	4.7	4	4.6	8	8.0
$\chi^2 = 11.83$; $p = 0.019$						
Gln-allele	79.8		87.9		75.0	
Glu-allele	20.2		12.1		25.0	
Late onset						
Genotype	Healthy weight, n = 68		Overweight, n = 119		Obesity, n = 95	
	n	%	n	%	n	%
Gln/Gln	29	42.6	38	31.9	43	45.3
Gln/Glu	36	52.9	59	49.6	41	43.2
Glu/Glu	3	4.4	22	18.5	11	11.5
$\chi^2 = 10.45$; $p = 0.03$						
Gln-allele	69.1		56.7		66.8	
Glu-allele	30.9		43.3		33.2	

Table 4. Obesity risk in BA patients with regard to the Gln27Glu polymorphism in the β_2 -adrenoceptor gene.

Model	P _{obs}	OR _{obs} (95% CI)	AIC
Early onset			
Dominant	0.13	1.57 (0.87–2.84)	16.87
Recessive	0.65	1.29 (0.43–4.06)	18.94
Super-dominant	0.18	1.52 (0.82–2.86)	16.77
Additive	0.18	1.37 (0.87–2.18)	17.31

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 β_2 -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 β_2 -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 β_2 -AR gene in the occurrence of not only BA, but also obesity. Thus, Jalba M.S. (2008) performed a meta-analysis of 41 studies involving genotyping results of more than 20,000 individuals on the role of the Gln27Glu polymorphism in the β_2 -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 β_2 -AR gene was associated with an increased risk of obesity in Gln/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 β_2 -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 β_2 -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 β_2 -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 β_2 -AR gene may play an important role in the development of obesity, energy expenditure, and lipolytic function of β_2 -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 β_2 -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 increased insulin levels, insulin resistance, and triglyceride level [26].

In our previous study on a smaller sample of BA patients ($n = 195$), we established a correlation between BMI and Gln/Gln, Gln/Glu, and Glu/Glu genotypes for the Gln27Glu polymorphism in the β_2 -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 β_2 -AR gene depending on BMI ($\chi^2 = 7.77$; $p = 0.1$). 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 β_2 -AR gene depending on the age of BA onset ($\chi^2 = 41.24$; $p = 0.001$) 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 (Glu/Glu+Gln/Glu) was 3.4 times higher than that in the major allele homozygotes ($p = 0.001$) [28]. The obtained data indicated that the minor allele carriers (both homozygotes and heterozygotes) 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 β_2 -AR gene in any inheritance model.

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 (Gln/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 β_2 -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 β_2 -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 β_2 -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 β_2 -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.

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