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Kadykova O., Borovyk K., Ryndina N.

Metabolic Status in Patients with Ischemic Heart Disease and Obesity with Different Genotypes of Leptin Receptor Gene (Arg223Glu)

Kharkiv National Medical University,
Kharkiv, Ukraine

The purpose of the study was to assess the metabolic status, namely carbohydrate and lipid metabolism, in patients with coronary heart disease and obesity with different genotypes of the leptin receptor gene (Arg223Glu).

Materials and methods. The study included 220 patients with coronary heart disease and obesity. The comparison group consisted of 113 patients with coronary heart disease with normal body weight. The control group included 35 healthy individuals. Additionally, patients with coronary heart disease and obesity were divided into subgroups depending on the genotype of the leptin receptor gene (Arg223Glu): the first subgroup included carriers of the A/A genotype (n=57), the second – G/A genotype (n=90), the third – G/G genotype (n=73).

Results and discussion. The analysis of carbohydrate metabolism depending on the genotypes of the leptin receptor gene (Arg223Gln) in patients with coronary heart disease and obesity showed that carriers of the G/G genotype have more pronounced disorders of carbohydrate metabolism in the form of hyperinsulinemia and decreased tissue sensitivity to insulin while carriers of the genotypes G/A and A/A have greater resistance to glucose-metabolic disorders. Body mass index in carriers of G/G genotype had the highest value, which is 19.19% and 19.53% more than in carriers of genotypes G/A and A/A. Thus, the G/G genotype in patients with coronary heart disease and obesity was associated with body mass index. The impaired lipid metabolism in patients with coronary heart disease in combination with obesity was defined as hypertriglyceridemia, which is associated with the G/G genotype of the leptin receptor gene polymorphism (Arg223Gln).

The results obtained in our work indicate the involvement of the polymorphic locus of the leptin receptor gene (Arg223Gln) in the formation of disorders of carbohydrate and lipid metabolism, which corresponds to the literature.

It has been suggested that structural changes in the leptin receptor gene are associated not only with the development of obesity but also with the development of type 2 diabetes mellitus.

Conclusion. The features of the combined course of coronary heart disease and obesity were identified: hyperinsulinemia and insulin resistance are associated with the G allele and G/G genotype of the polymorphic locus Arg223Gln leptin receptor gene (r=0.76, p<0.05); the rearrangement of the lipid spectrum due to hypertriglyceridemia is influenced by the homogeny of the G allele of the polymorphic locus of the Arg223Gln gene of the leptin receptor gene (r=0.73, p<0.05).

Keywords: leptin receptor gene, coronary heart disease, obesity, insulin resistance.

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Introduction. Recent studies in cardiology have shown the effect of leptin on the occurrence and progression of cardiovascular disease, due to its correlation with cardiovascular risk factors such as lipid concentration, blood pressure, hemostasis and inflammation [1, 2]. It has been described that hyperleptinemia is an independent predictor of cardiac events in patients with coronary heart disease (CHD), a marker of risk stratification in unstable angina and a factor in the development of acute coronary syndrome [3].

Leptin is encoded by the leptin gene, in humans it is localized on chromosome 7a31.3, consists of three exons separated by two nitrons [4]. The leptin gene is one of the most intensively studied candidate genes for obesity in humans [5, 6]. Rare mutations (F17L, VI UM) and polymorphism (C-188A) of the leptin receptor gene have been described in the literature [7, 8].

In a study by J. Hager and co-authors in 1998, it was found [9] that homozygotes for the 19G allele have lower levels of leptin than carriers of the 19A allele. W.D. Li and co-authors found in 1999 [10] that A19G leptin receptor gene polymorphism was a predictor of obesity (heterozygotes had a higher body mass index (BMI) than homozygotes for the 19A and 19G alleles), although other studies have not found this.

However, a number of studies have found no differences between leptin levels and associations with BMI, waist circumference (WC) / hip circumference (HC) ratio, body weight and body fat weight in carriers of different genotypes leptin receptor gene [10, 11].

An important role in the investigation of the mechanisms of leptin resistance is assigned to genetic research to study leptin receptor gene polymorphisms. It is believed that a number of leptin receptor gene polymorphisms may play an important role in the regulation of this receptor and in the pathophysiological mechanisms of obesity.

Several polymorphisms of the leptin receptor gene are currently known: Q223R, K656N, K109R, T34SZ, G 1019A. Among them, A668G polymorphism is the most frequently studied. A668G polymorphism is localized in exon 6 of the extracellular region of the leptin receptor in the C domain, which has a leptin-binding zone and leads to a single amino acid substitution of glutamine (Gln) to arginine (Arg) in codon 223 and causes measurement of 14 functional receptor activity [12]. In the literature, this polymorphism is most often referred to as Q223R, and allelic forms of the leptin receptor gene are referred to as 223Q and 223R. The prevalence of alleles differs significantly in different countries and ethnic groups, in particular, the frequency of 223R allele for Asians is much higher than for other ethnic groups – up to 0.85 [13]. The prevalence of the 223R allele in healthy Europeans according to various authors ranges from 0.41 (England) to 0.44 (Netherlands) [14, 15].

A number of studies have found that carrying the 223R receptor gene allele to leptin is associated with high levels of circulating leptin and decreased leptin receptor sensitivity [16, 17], as well as BMI [18, 19]. Other researchers have reported an association of the R223 allele with glucose and insulin levels [20, 21]. M.G.V. Gottlieb and co-authors in 2009 linked this polymorphism to MS: Q223Q and Q223R genotypes were more common in patients with metabolic syndrome than in healthy people [22].

Carriers of the 223R allele of the leptin receptor gene (homozygotes for the 223R allele and heterozygotes) were found to be associated with combined hyperlipidemia, decreased insulin sensitivity and obesity [23].

However, a study by A. Constantin and co-authors in 2010 did not establish a link between Q223R polymorphism and indicators such as BMI and blood pressure [24]. A. Lakka and co-authors in 2004 also found no link between insulin resistance (IR) and leptin receptor gene polymorphism [23].

Thus, the results of studies studying the polymorphisms of the leptin receptor gene and the leptin receptor are contradictory. Further studies are needed to determine the association of leptin receptor gene polymorphisms with leptin levels, obesity, and IR, as well as the risk of cardiovascular disease and chronic heart failure.

The purpose of the study was to assess the metabolic status, namely carbohydrate and lipid metabolism, in patients with coronary heart disease and obesity with different genotypes of the leptin receptor gene (Arg223Glu).

Materials and methods. For the purpose of the study, a comprehensive examination of 220 patients with coronary heart disease and obesity who were treated in the cardiology department of the Kharkiv City Clinical Hospital No. 27, which is the basic medical institution of the Department of Internal Medicine No. 2, Academician L. T. Malaya clinical immunology and allergology of Kharkiv National Medical University. The comparison group consisted of 113 patients with coronary heart disease with normal body weight. The control group included 35 healthy individuals. Additionally, patients with coronary heart disease and obesity were divided into subgroups depending on the genotype of the leptin receptor gene (Arg223Glu): the first subgroup included carriers of the A/A genotype (n=57), the second – G/A genotype (n=90), the third – G/G genotype (n=73). The groups were comparable in age and gender. The study did not include patients with severe comorbidities of the respiratory and digestive system organs, kidney damage and cancerous subjects.

The diagnosis was established in accordance with the current orders of the Ministry of Health of Ukraine.

All patients underwent general clinical and instrumental examinations. In order to control carbohydrate metabolism, glucose levels were determined by glucose oxidation method; determination of glycosylated hemoglobin (HbA1c) content in whole blood was performed by photometric reaction with thiobarbituric acid using a commercial test system from Reagent (Ukraine) according to appendix. Insulin concentration was determined by enzyme-linked immunosorbent assay using the commercial test system INSULIN ELISA KIT manufactured by Monobind (USA). We used the HOMA (Homeostasis Model Assessment) IR index, which was calculated by the formula:

insulin (μU/ml) × fasting glucose (mmol/l)/22.5

At HOMA index >2.77 patients were considered insulin resistant.

The biochemical study includes the determination of total cholesterol (TC) and high-density lipoprotein (HDL) by the peroxidase method using the Cholesterol Liquicolor reagent kit by Human (Germany) in heparin-stabilized serum. The level of triglycerides (TG) was determined by enzymatic colorimetric method

using a set of reagents “Triglycerides GPO” by Human (Germany). The coefficient of atherogenicity (CA) was calculated according to the formula of Klimov A. M.: CA = (CKD – HDL)/HDL; the level of very low density lipoproteins (VLDL) = TG/2.2×0.45, (mmol/l); the level of low-density lipoproteins (LDL) = = CHD – (VLDL + HDL), (mmol/l).

The study determined the anthropometric indicators of WC and HC, neck circumference (NC). To characterize obesity BMI (Kettle index) was determined, which was calculated by the formula:

weight (kg) / height (m^2)

Studies of the allelic polymorphism of the Arg223Gln gene of the leptin receptor were performed by polymerase chain reaction with electrophoretic detection of results using reagent sets “SNP-EXPRESS” manufactured by SPE “Litech”. The correctness of the genotype frequency distribution was determined by the correspondence of the equilibrium of G. Hardy-B. Weinberg (pi2 + 2 pipj + pj2 = 1).

The studies were approved by the commission on biomedical ethics of Kharkiv National Medical University (protocol No. 2, dated 12.10.2022) and were conducted in accordance with the written consent of the participants and in accordance with the principles of bioethics set forth in the Helsinki Declaration “Ethical Principles of Medical Research Involving Humans” and the “Universal Declaration on Bioethics and Human Rights (UNESCO)”.

Statistical data processing was performed using the Statistica package, version 10.0. Pearson’s and Fisher’s χ2 criteria were used to compare the distribution of allele and genotype frequencies between groups. To determine the relative risk of disease, the odds ratio (OR) was calculated. As the absence of associations was considered OR = 1; as a positive association – OR >1; as a negative association of an allele or genotype with the disease (low risk of disease) was considered OR < 1. Confidential interval (CI) is the range of values, within which there is a 95% probability of the prognostic value of OR. Differences at p<0.05 were considered statistically significant.

Results and discussion. Analysis of carbohydrate metabolism revealed that in patients with coronary heart disease and obesity carriers of A/A genotype of the leptin receptor gene (Arg223Gln) glucose level was 4.48 ± 0.08 mmol/l, insulin level – 7.09 ± 0.83 – 13.23 ± 0.79 μU/ml, glycosylated hemoglobin – 5.07 ± 0.28%, HOMA-IR index – 1.42 ± 0.44 units; in carriers of G/A genotype – 4.52 ± 0.06 mmol/l, 7.52 ± 0.70 μU/ml, 5.10 ± 0.23%, 1.54 ± 0.35 units, respectively; in G/G genotype group the above mentioned indicators corresponded values – 4.59 ± 0.16 mmol/l, 11.17 ± 0.68 μU/ml, 5.24 ± 0.28% and 2.77 ± 0.44 units (**Table 1**).

Table 1 – Indicators of carbohydrate metabolism in patients with coronary heart disease and obesity depending on the genotypes of polymorphism of the leptin receptor gene (Arg223Gln) (M ± m)

Indexes	Leptin receptor gene genotypes (Arg223Gln)			p
	G/G (n=73)	G/A (n=90)	A/A (n=57)	
HOMA, units	2.77 ± 0.44	1.54 ± 0.35	1.42 ± 0.44	p_{1-2}<0.05 p_{1-3}<0.05 p_{2-3} >0.05
HbA_{1c},%	5.24 ± 0.28	5.10 ± 0.23	5.07 ± 0.28	p_{1-2} >0.001 p_{1-3} >0.001 p_{2-3} >0.001
Blood glucose, mmol/l	4.59 ± 0.16	4.52 ± 0.06	4.48 ± 0.08	p_{1-2} >0.001 p_{1-3} >0.001 p_{2-3} >0.001
Insulin, μU/ml	11.17 ± 0.68	7.52 ± 0.70	7.09 ± 0.83	p_{1-2}<0.001 p_{1-3}<0.001 p_{2-3} >0.001

Comparison of carbohydrate metabolism versus different genotypes of the leptin receptor gene (Arg223Gln) in patients with coronary heart disease and obesity showed that patients with G/G genotype had significantly higher values of insulin and HOMA-IR index. Insulin levels were higher in patients with G/G genotype by 32.56% and 36.67% than in patients with G/A and A/A genotypes, and HOMA IR index by 44.93% and 48.91%, respectively (p <0.05). There were no significant differences in glucose and glycosylated hemoglobin levels depending on the genotypes of the leptin receptor gene (Arg223Gln) (p >0.001).

Thus, analysis of carbohydrate metabolism depending on the genotypes of the leptin receptor gene (Arg223Gln) in patients with coronary heart disease and obesity showed that carriers of the G/G genotype have more pronounced disorders of carbohydrate metabolism in the form of hyperinsulinemia and decreased tissue sensitivity to insulin while carriers of the genotypes G/A and A/A have greater resistance to glucose-metabolic disorders. The obtained data suggest that the G allele in the homozygous position is a pathological variant of the polymorphism of the leptin receptor gene (Arg223Gln) and the allele A has a protective effect.

As can be seen from **Table 2** WC, HC, NC and WC/HC ratio did not differ in patients with coronary

Table 2 – Status of constitutional indicators in patients with coronary heart disease and obesity depending on the genotypes of leptin receptor gene polymorphism (Arg223Gln) (M ± m)

Parameters	Genotypes of leptin receptor gene polymorphisms (Arg223Gln)			p
	G/G (n=73)	G/A (n=90)	A/A (n=57)	
WC, cm	113.77 ± 1.42	113.22 ± 1.39	112.74 ± 1.46	p_{1-2} >0.05 p_{1-3} >0.05 p_{2-3} >0.05
HC, cm	113.07 ± 1.54	113.02 ± 1.46	112.33 ± 1.45	p_{1-2} >0.05 p_{1-3} >0.05 p_{2-3} >0.05
WC/HC ratio	1.01 ± 0.005	1.00 ± 0.002	1.00 ± 0.003	p_{1-2} >0.05 p_{1-3} >0.05 p_{2-3} >0.05
BMI, kg/m^2	38.51 ± 0.57	31.21 ± 0.67	31.05 ± 0.55	p_{1-2}<0.001 p_{1-3}<0.001 p_{2-3} >0.001
NC, cm	49.24 ± 0.82	48.91 ± 0.70	49.07 ± 1.04	p_{1-2} >0.05 p_{1-3} >0.05 p_{2-3} >0.05

heart disease and obesity depending on the genotypes of the leptin receptor gene (Arg223Gln) (p >0.05).

BMI in carriers of G/G genotype had the highest value (38.51 ± 0.57 kg/m^2), which is 19.19% and 19.53% more than in carriers of genotypes G/A and A/A, where the values of this indicator were 31.21 ± 0.67 kg/m^2 and 31.05 ± 0.55 kg/m^2, respectively (p<0.001). Thus, the G/G genotype in patients with coronary heart disease and obesity was associated with BMI.

Assessing lipid metabolism in patients with coronary heart disease and obesity, it should be noted that all indicators exceeded the normative values due to the contribution of coronary heart disease and obesity in the restructuring of lipid metabolism due to pathogenetic factors (**Table 3**).

Significant differences in the levels of TC, HDL, LDL, VLDL and CA depending on the genotypes of the leptin receptor gene (Arg223Gln) in patients with coronary heart disease and obesity were not found (p >0.05). The level of TC in carriers of genotype A/A was 5.45 ± 0.08 mmol/l, HDL – 1.13 ± 0.06 mmol/l, LDL – 3.50 ± ± 0.09 mmol/l, VLDL – 1.82 ± 0.06 mmol/l, CA – 4.78 ± 0.07. In patients with the G/A genotype the level of TC was 5.47 ± ± 0.07 mmol/l, HDL – 1.07 ± 0.05 mmol/l, LDL – 3.57 ± 0.07 mmol/l, VLDL – 1.87 ± ± 0.07 mmol/l, CA – 4.81 ± 0.06. In patients with G/G genotype the level of TC was 5.58 ± 0.06 mmol/l, HDL – 0.96 ± ± 0.04 mmol/l, LDL – 3.61 ± 0.05 mmol/l, VLDL – 1.90 ± 0.06 mmol/l, CA – 4.90 ± 0.09.

The level of TG in the group of patients with G/G genotype was probably higher by 34.02% and 36.93% than in patients with genotypes G/A and A/A, (p<0.05).

Thus, impaired lipid metabolism in patients with coronary heart disease in combination with obesity was defined as hypertriglyceridemia, which is associated with the G/G genotype of the leptin receptor gene polymorphism (Arg223Gln).

Studies of the nature of the relationships between the indicators and the genotypes of the leptin receptor gene (Arg223Gln) in patients with coronary heart disease and obesity are presented in **Table 4**. Direct correlations between the G/G genotype and insulin levels were determined (r=0.76, p<0.05), BMI (r=0.84, p<0.05), TG (r=0.73, p<0.05).

The results obtained in our work indicate the involvement of the polymorphic locus of the leptin receptor gene (Arg223Gln) in the formation of disorders of carbohydrate and lipid metabolism, which corresponds to the literature.

Table 3 – Indicators of lipid metabolism in patients with coronary heart disease and obesity depending on the genotypes of leptin receptor gene polymorphism (Arg223Gln) (M ± m)

Parameters	Genotypes of leptin receptor gene polymorphisms (Arg223Gln)			p
	G/G (n=73)	G/A (n=90)	A/A (n=57)	
TC, mmol/l	5.58 ± 0.06	5.47 ± 0.07	5.45 ± 0.08	p_{1-2} >0.05 p_{1-3} >0.05 p_{2-3} >0.05
TG, mmol/l	2.41 ± 0.09	1.59 ± 0.08	1.52 ± 0.07	p_{1-2}<0.05 p_{1-3}<0.05 p_{2-3} >0.05
HDL, mmol/l	0.96 ± 0.04	1.07 ± 0.05	1.13 ± 0.06	p_{1-2} >0.05 p_{1-3} >0.05 p_{2-3} >0.05
LDL, mmol/l	3.61 ± 0.05	3.57 ± 0.07	3.50 ± 0.09	p_{1-2} >0.05 p_{1-3} >0.05 p_{2-3} >0.05
VLDL, mmol/l	1.90 ± 0.06	1.87 ± 0.07	1.82 ± 0.06	p_{1-2} >0.05 p_{1-3} >0.05 p_{2-3} >0.05
CA	4.90 ± 0.09	4.81 ± 0.06	4.78 ± 0.07	p_{1-2} >0.05 p_{1-3} >0.05 p_{2-3} >0.05

Table 4 – Matrix of intercorrelations between indicators of carbohydrate, lipid metabolism and genotypes of leptin receptor gene polymorphism (Arg223Gln) in patients with coronary heart disease and obesity (r_{crit}=0.24)

Genotype / Parameter	G/G	G/A	A/A
Glucose	0.13	0.18	–0.15
Insulin	0.76*	0.20	–0.17
HOMA	0.23	0.22	–0.21
HbA_{1c}	0.17	0.13	–0.14
BMI	0.84*	0.18	–0.23
WC	0.20	0.17	–0.16
HC	0.18	0.06	–0.11
WC/HC	0.19	0.09	–0.02
TC	0.09	0.17	–0.12
TG	0.73*	0.19	–0.17
HDL	0.22	0.20	0.15
LDL	0.11	0.17	–0.19
VLDL	0.08	0.08	–0.13
CA	0.10	0.15	–0.14

Note: *p<0.05, r_{crit}=0.24

Some researchers have shown a relationship between BMI and the carrier of the A/A genotype [25], as well as the A allele with higher levels of TG, glucose and blood pressure [26], other studies have not found an association between polymorphism of this gene and obesity [27-29], and in the study of polymorphism of this gene in the inhabitants of the Pacific Islands, the "protective" effect of the A allele in obesity was shown.

It has been suggested that structural changes in the leptin receptor gene are associated not only with the development of obesity but also with the development of type 2 diabetes mellitus (DM). Thus, The Finnish Diabetes Prevention Study found that two polymorphisms (Q223R, Lysl09Arg) of the leptin receptor gene were predictors of type 2 diabetes mellitus in patients with glucose intolerance [28]. Also, several researchers have obtained data on the association of the 223R allele with the levels of TG, glucose and insulin [29].

However, in the work of T. Gotoda and co-authors [30] and in the results of a meta-analysis, performed by M. Neo and co-authors [31], no association of Q223R polymorphism of the leptin receptor gene polymorphism with type 2 diabetes mellitus was found.

Conclusion

1. The features of the combined course of coronary heart disease and obesity were identified: hyperinsulinemia and insulin resistance are associated with the G allele and G/G genotype of the polymorphic locus Arg223Gln leptin receptor gene (r=0.76, p<0.05).
2. The rearrangement of the lipid spectrum due to hypertriglyceridemia is influenced by the homogeny of the G allele of the polymorphic locus of the Arg223Gln gene of the leptin receptor gene (r=0.73, p<0.05).

Perspectives of further research. In connection with the high frequency of the comorbid course of coronary heart disease and obesity, as well as the increase in mortality and fatal and non-fatal cardiovascular complications in these patients, the search for early diagnostics opportunities is an urgent issue today.

Information on conflict of interest: there is no conflict of interest.

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МЕТАБОЛІЧНИЙ СТАТУС У ХВОРИХ НА ІШЕМІЧНУ ХВОРОБУ СЕРЦЯ ТА ОЖИРІННЯ З РІЗНИМИ ГЕНОТИПАМИ ГЕНА РЕЦЕПТОРУ ЛЕПТИНА (Arg223Glu)

Кадикова О. І., Боровик К. М., Риндіна Н. Г.

Резюме. *Метою дослідження* було оцінити метаболічний статус, а саме вуглеводний та ліпідний обміни, у хворих на ішемічну хворобу серця та ожиріння з різними генотипами гена рецептора лептину (Arg223Glu).

Матеріали та методи. Обстежено 220 хворих на ішемічну хворобу серця та ожиріння, групу порівняння склали 113 хворих на ішемічну хворобу серця з нормальною масою тіла. Контрольну групу склали 35 здорових осіб. Додатково пацієнтів з ішемічною хворобою серця та ожирінням розподілили на підгрупи залежно від генотипу гена рецептора лептину (Arg223Glu): до першої підгрупи увійшли носії A/A генотипу (n=57), до другої – G/A генотипу (n=90), до третьої – G/G генотипу (n=73).

Результати. Аналіз вуглеводного обміну залежно від генотипу гена рецептора лептину (Arg223Gln) у хворих на ішемічну хворобу серця та ожиріння показав, що у носіїв генотипу G/G більш виражені порушення вуглеводного обміну у вигляді гіперінсулінемії та зниження тканинної чутливості до інсуліну, тоді як носії генотипів G/A та A/A мають більшу резистентність до глюкозометаболічних порушень. ІМТ у носіїв G/G генотипу мав найбільше значення (38,56±0,58 кг/м^2), що на 19,19 % і 19,53 % більше, ніж у носіїв генотипів G/A і A/A, де значення цього показника склали 31,16±0,62 кг/м^2, 31,03±0,56 кг/м^2 відповідно ($p<0,001$). Отже, генотип G/G у хворих на ІХС й ожирінням був пов'язаний з ІМТ. Вірогідних відмінностей щодо рівнів ЗХС, ХС ЛПВЩ, ХС ЛПНЩ, ХС ЛПДНЩ і КА у залежності від генотипів гена рецептору лептина (Arg223Gln) у хворих на ІХС й ожиріння встановлено не було ($p >0,05$). Порушення ліпідного обміну у хворих на ІХС у поєднанні з ожирінням визначалось у вигляді гіпертригліцеридемії, яка асоційована з G/G генотипом поліморфізму гена рецептору лептина (Arg223Gln).

Висновки. Виявлено особливості поєднаного перебігу ішемічної хвороби серця та ожиріння: гіперінсулінемія та інсулінорезистентність пов'язані з алелем G та генотипом G/G поліморфного локусу гена рецептора лептину Arg223Gln ($r=0,76$, $p<0,05$); на перебудову ліпідного спектру внаслідок гіпертригліцеридемії впливає гомогенність алеля G поліморфного локусу гена Arg223Gln гена рецептора лептину ($r=0,73$, $p<0,05$).

Ключові слова: ген рецептора лептину, ішемічна хвороба серця, ожиріння, інсулінорезистентність.

ORCID and contributionship:
Olga Kadykova : 0000-0002-0108-0597 A,D
Kateryna Borovyk : 0000-0003-2155-4865 B,C
Natalia Ryndina : 0000-0003-2731-4491 E,F

A – Work concept and design, B – Data collection and analysis,
C – Responsibility for statistical analysis, D – Writing the article,
E – Critical review, F – Final approval of the article

CORRESPONDING AUTHOR
Kateryna Borovyk
Kharkiv National Medical University,
Department of Internal Medicine No. 2,
clinical Immunology and Allergology Named after Academician L.T. Malaya
4, Nauky Ave., Kharkiv 61001, Ukraine
phone: +380636834442, e-mail: borovyk.kateryna@gmail.com

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