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Short Communication **Open Access**

Heart and vascular remodeling in essential hypertension and type 2 diabetes is dependent on genetic polymorphisms

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ABSTRACT

Aim: To study heart and vascular remodeling in essential hypertension (EH) and concomitant type 2 diabetes mellitus (DM2) with respect to genetic polymorphism of the angiotensin II receptor type 1 (*AGTR1*) gene and peroxisome proliferator-activated receptor-γ2 (*PPARγ2*). **Methods:** Biochemical blood analysis, echocardiographic evaluation of mitral diastolic blood flow and tissue Doppler spectral modes, reactive hyperemia, color Doppler mapping. **Results:** Patients with *A/C* and *C/C* genotypes of the *AGTR1* gene had higher blood pressure, more pronounced metabolic disorders, a larger left ventricle (LV), higher myocardial mass index left ventricle, and a greater intima media thickness (IMT), with a lower rate of endothelium-dependent vasodilation (EDVD) compared to the *A/A* genotype. Patients with the *Pro/Pro* genotype of *PPARγ2* had higher levels of blood pressure, larger LVs, greater IMT, pulse wave velocity, and a lower rate of EDVD compared to the *Pro/Ala* and *Ala/Ala* genotypes. Patients with the *Pro/Pro* genotype had significantly more pronounced dyslipidemia and insulin resistance than patients with other *PPARγ2* genotypes. **Conclusion:** The polymorphism of genetic markers *AGTR1* and *PPARγ2* in patients with EH and concomitant DM2 was associated with the development of comorbidity. Different genotypes of specific genes alter the severity of cardiovascular remodeling and metabolic disorders.

Quick Response Code:

INTRODUCTION

There are a large number of patients with essential hypertension (EH) who also have type 2 diabetes mellitus (DM2), thus meriting further research into this problem. It is known that EH and DM2 have many common pathogenetic mechanisms that affect the development of comorbidity. According to many researchers, the most important predictors of EH and DM2 are hereditary risk factors.[1-3] However, there are controversial views on the role of gene expression and genetic polymorphisms in the development and course of diseases in different populations of patients, as well as their influence on the effectiveness of drug therapy.

Some studies have shown that the predisposing cause of EH can be mutational alleles of the angiotensin II receptor (*AGTR1*) gene; angiotensin is a powerful vasoconstrictor, thus playing a role in the pathogenesis of EH.[4,5] Angiotensin II (AT-II) receptor type 1, which is located on the vascular endothelium, mediates the main cardiovascular effects of angiotensin, including the induction of insulin-like growth factor and endothelin-1. The induction of cell growth is also mediated through *AGTR1*.[6] A number of investigations have reported that *AGTR1* polymorphisms may lead to changes in the regulation of vascular tone and proliferation of vascular wall elements.[7]

Hyperinsulinemia and insulin resistance (IR) are the factors that determine the frequency of cardiovascular complications in DM2.[8-10] Despite the fact that IR has a clearly identified genetic predisposition, its underlying genetic disorders have still not been identified.

There has been extensive research into the polymorphisms of peroxisome proliferator-activated receptors (*PPAR*), which are transcription factors that control the activity of many genes, as well as regulating lipid and carbohydrate metabolism.[11,12] Here we focused on *PPARγ2*, which is almost exclusively located in adipose tissue, and plays a vital role in controlling adipogenesis and circulation of fatty acids.

It has been established that genetic polymorphisms of *PPARγ2* are different in diverse populations, and data on the effect of *PPARγ2* on the development of IR are quite controversial. Therefore, there is a continued interest by scientists into the study of *PPARγ2* polymorphisms in the development of IR and other pathological processes, and the presence of conflicting data regarding its role in different populations justifies the ongoing research into the Ukrainian population of patients with comorbid disorders.

Our aim was to study heart and vascular remodeling in patients with EH and concomitant DM2 according to the genetic polymorphisms of *AGTR1* and *PPARγ2*.

METHODS

The authors examined 320 patients with EH stage II grade 2 and moderate, sub-compensated DM2 (the main group); 90 patients with EH stage II grade 2 without DM2 (the comparison group); and 31 healthy individuals (the control group).

In this study, using standard biochemical methods on the patients, we defined venous blood glucose concentration, glycosylated hemoglobin (HbA1c), and insulin levels. IR was determined using the homeostasis model assessment index (HOMA-IR). Ultrasound examinations were performed on a cardiac ultrasound scanner («ULTIMA RA» firm "RADMIR", Ukraine) in one-, two-dimensional and Doppler modes with color mapping by conventional methods. The following measurements were made: volumes of the left atrium (LA) and right atrium (RA); end-systolic diameter (ESD) and end-diastolic diameter (EDD) of the left ventricle (LV); end-diastolic pressure (EDP) in the LV; left ventricular ejection fraction (EF); index of relative wall thickness (IRWT); and the myocardial mass index (MMI) of the LV. Diastolic function of the LV was assessed by studying the blood flow in the pulmonary artery and transmitral diastolic flow in the pulsed Doppler mode with the following parameters: maximum rate of early LV filling (E); maximum speed of late (atrial) LV filling (A); the ratio of the maximum velocity of early and late LV filling (E/A); LV isovolumic relaxation time (IVRT); deceleration time (DT) of early diastolic flow velocity; average pulmonary artery pressure (PAP), according to Kitabatake; the ratio of peak E and e on the mitral valve in the spectral and tissue Doppler (E/e). For studying endothelial function, the degree of endothelium-dependent vasodilation (EDVD) in reactive hyperemia was determined in all patients. Investigations were carried out using a broadband linear transducer 5-12 MHz Doppler color mapping with three readings being taken arteries at 15-min intervals between samples on the left and right brachial arteries, according to the method of Celermajer DS (a modification of the method by Ivanova OV). Normally, the maximum vasodilation of the brachial artery should exceed 10% of the original diameter. Simultaneously, we measured the intima media thickness (IMT) of the carotid artery (CA 2 cm proximal to the bifurcation of the common carotid artery). Pulse wave velocity (PWV) of the CA was determined using the W-Track-method (method of phase tracking, patented scanner developers). Determining the PWV of the abdominal aortic (AA) (on the left subclavian artery to the femoral

artery) was performed using a phased transducer with a frequency of 2-4 MHz. An *A1166C* polymorphism of the *AGTR1* gene and a *Pro12Ala* polymorphism of the *PPARγ2* gene were assessed by the molecular genetic method. Three genotypes of the *AGTR1* gene (*A/A*, *A/C* and *C/C*) were identified, along with three genotypes of the *PPARγ2* gene (*Pro/Pro*, *Pro/Ala* and *Ala/Ala*). Processing of statistical data was performed using the software package "Statistics for Windows 6.0". The values are presented as the average value of parameters (M) and standard error (m).

The study protocol was approved by the Ethics Committee of the Kharkiv National Medical University. All participants were informed about the aim of the study and signed a written consent form.

RESULTS

Evaluation of the *A1166C* polymorphism of the *AGTR1* gene in patients with comorbidity of EH and DM2, compared to the distribution of alleles and genotypes in healthy individuals, and in patients with EH but without DM2, showed that 61.6% of patients with EH and DM2, and 57.8% of patients with EH without DM2, had *A/C* and *C/C* genotypes of *AGTR1*, which have been shown to be associated with cardiovascular complications by some researchers.[9,10] The genotypes of the main group ($P < 0.01$) and the comparison group ($P < 0.05$) were significantly different from the control group. The *C* allele was established in 33.1% of patients with EH and DM2, and 31.1% of patients with EH without DM2; in the control group, the *C* allele was significantly less present ($P < 0.05$) [Table 1].

In the next step of the study, hemodynamic and metabolic parameters in patients with comorbidity of EH and DM2, in different polymorphism variants of the *AGTR1* gene, were compared [Table 2].

Patients with *A/C* and *C/C* genotypes of the *AGTR1* gene had higher blood pressure ($P < 0.001$) compared to the *A/A* genotype. These patients also had significantly larger LV and myocardial mass index left ventricle (MMILV), and a greater IMT, with a lower rate of EDVD. Patients with the indicated genotypes also had significantly more pronounced metabolic disorders than patients with the *A/A* genotype. No significant differences in hemodynamic and metabolic parameters between the *C/C* and *A/C* genotypes were found [Table 2].

Given that *A/C* and *C/C* genotypes presented significantly different characteristics from the *A/A* genotype, with more severe disorders of echocardiographic and biochemical parameters, but were not significantly different from each other, in the next step of the study, patients with *A/C* and *C/C* genotypes were merged into a single group, namely the *A/C* + *C/C* genotype.

For establishing associations of *AGTR1* polymorphisms with cardiovascular remodeling, a comparative evaluation of echocardiographic parameters and indicators of the structural and functional state of the heart and blood vessels of the main group of patients, with different genotypes, was performed [Table 3]. It was found that patients with the *A/C* + *C/C* genotype had significantly larger LV compared to the *A/A* genotype ($P < 0.01$). Thus, patients with the *A/C* + *C/C* genotype also had significantly ($P < 0.05$) greater MMILV compared to the *A/A* genotype. In addition, the *A/C* + *C/C* genotype had significantly ($P < 0.05$) lower values of the diastolic function indicator E/A.

Assessment of the great vessels showed that IMT in the main group of patients with the genotype *A/C* + *C/C* was significantly ($P < 0.001$) greater than the genotype *A/A* [Table 3]. The study did not reveal any significant differences in PWV values in the carotid artery or the abdominal aorta in the diverse *AGTR1* genotypes. It should be noted that in patients with EH with concomitant DM2 and genotype *A/C* + *C/C*, the level of EDVD was significantly ($P < 0.001$) lower than the genotype *A/A*.

In the next step of the study, the *Pro12Ala* polymorphism of *PPARγ2* was estimated and compared with the distribution of alleles and genotypes in healthy individuals and in patients with EH without DM2 [Table 4].

It was found that, in all study groups, patients with the *Pro* allele were predominant (86.6% in the main group, 85.6% in the comparison group and 87.1% in

Table 1: The distribution of *AGTR1* alleles and genotypes in the patients, *n* (%)

Indices	Main group ($n = 320$)	Comparison group ($n = 90$)	Control group ($n = 31$)
A allele	214 (66.9)*	62 (68.9)*	25 (80.6)
C allele	106 (33.1)*	28 (31.1)*	6 (19.4)
A/A genotype	123 (38.4)*	38 (42.2)*	20 (64.5)
A/C genotype	182 (56.9)*	49 (54.5)*	10 (32.3)
C/C genotype	15 (4.7)	3 (3.3)	1 (3.2)

*$P < 0.05$ *vs.* the control group

Table 2: Comparative evaluation of hemodynamic and metabolic parameters in patients of the main group depending on genotypes of the *AGTR1* gene

Indices	Main group (*n* = 320)		
	***A/A* (*n* = 123)**	***A/C* (*n* = 182)**	***C/C* (*n* = 15)**
SBP, mmHg	166.041 ± 0.261	173.821 ± 0.221*	172.401 ± 0.621*
DBP, mmHg	99.461 ± 0.181	102.041 ± 0.231*	102.331 ± 0.851*
EDD LV, cm	4.911 ± 0.031	5.031 ± 0.031*	5.161 ± 0.095*
ESD LV, cm	3.221 ± 0.031	3.321 ± 0.031*	3.421 ± 0.091*
MMI LV, g/m	134.571 ± 2.391	143.931 ± 3.09*	146.611 ± 3.791*
E/A	0.950 ± 0.021	0.897 ± 0.015*	0.981 ± 0.021
E/e	6.223 ± 0.104	6.411 ± 0.251	6.661 ± 0.291
IMT, mm	0.914 ± 0.009	0.953 ± 0.007*	0.969 ± 0.024*
PWV of the CA, m/c	8.736 ± 0.097	8.870 ± 0.087	9.033 ± 0.333
PWV of the AA, m/c	8.866 ± 0.118	9.013 ± 0.099	9.109 ± 0.354
EDVD, %	6.657 ± 0.077	6.211 ± 0.065*	6.187 ± 0.242*
blood glucose, mmol/L	6.933 ± 0.052	7.046 ± 0.0291*	7.201 ± 0.025*
HbA1c, %	6.993 ± 0.044	7.011 ± 0.0361*	7.104 ± 0.015*
insulin, mcU/mL	23.249 ± 0.416	24.982 ± 0.291*	26.840 ± 0.994*
HOMA-IR	7.272 ± 0.130	7.991 ± 0.097*	8.276 ± 0.324*

*$P < 0.05$ *vs.* the *A/A* genotypes. SBP: systolic blood pressure; DBP: diastolic blood pressure; EDD LV: end-diastolic diameter of left ventricle; ESD LV: end-systolic diameter of left ventricle; MMI LV: myocardial mass index of left ventricle; E/A: ratio of the maximum velocity of early and late left ventricle filling; E/e: ratio of peak e and E on the mitral valve in the spectral and tissue Doppler; IMT: intima media thickness; PVW CA: pulse wave velocity by the carotid artery; PVW AA: pulse wave velocity by the abdominal aortic; EDVD: endothelium dependent vasodilation; HOMA-IR: homeostasis model assessment index

Table 3: Structural and functional state of heart and vessels in patients of the main group depending on genotypes of the *AGTR1* gene

Indices	Main group (*n* = 320)	
	***A/A* (*n* = 123)**	***A/C* + *C/C* (*n* = 197)**
EDD LV, cm	4.911 ± 0.031	5.040 ± 0.030*
ESD LV, cm	3.221 ± 0.031	3.326 ± 0.027*
MMI LV, g/m	134.571 ± 3.391	144.138 ± 2.965*
E/A	0.951 ± 0.021	0.903 ± 0.014*
E/e	6.223 ± 0.104	6.411 ± 0.151
IMT, mm	0.914 ± 0.009	0.952 ± 0.007*
PWV of the CA, m/c	8.736 ± 0.097	8.883 ± 0.084
PWV of the AA, m/c	8.866 ± 0.118	9.020 ± 0.095
EDVD, %	6.657 ± 0.077	6.180 ± 0.062*

*$P < 0.05$ *vs.* the *A/A* genotypes. EDD LV: end-diastolic diameter of left ventricle; ESD LV: end-systolic diameter of left ventricle; MMI LV: myocardial mass index of left ventricle; E/A: ratio of the maximum velocity of early and late left ventricle filling; E/e: ratio of peak e and E on the mitral valve in the spectral and tissue Doppler; IMT: intima media thickness; PVW CA: pulse wave velocity by the carotid artery; PVW AA: pulse wave velocity by the abdominal aortic; EDVD: endothelium dependent vasodilation

Table 4: Distribution of *PPARγ2* alleles and genotypes in the patients, *n* (%)

Indices	Main group (*n* = 320)	Comparison group (*n* = 90)	Control group (*n* = 31)
Pro allele	277 (86.6)	77 (85.6)	27 (87.1)
Ala allele	43 (13.4)	13 (14.4)	4 (12.9)
Pro/Pro genotype	242 (75.6)	67 (74.4)	24 (77.4)
Pro/Ala genotype	71 (22.2)	21 (23.3)	6 (19.4)
Ala/Ala genotype	7 (2.2)	2 (2.3)	1 (3.2)

the control group). It was also demonstrated that, in the main group and the comparison group, there were no significant differences in the frequency of different variants of the *PPARγ2* genotype. In both these patient groups, the *Pro/Pro* genotype was predominant, with a frequency of 75.6% and 74.4%, respectively. The homozygous genotype *Ala/Ala* was only found in 2.2% of the main group of patients and 2.3% of the comparison group of patients ($P > 0.05$). In the control group of patients, the *Pro/Pro* genotype was also prevalent (77.4% of cases); *Pro/Ala* and *Ala/Ala* genotypes were found in 19.4% and 3.2% of control patients, respectively. A similar distribution of *PPARγ* genotypes, according to other researchers[13] was inherent in the European population.

Comparison of hemodynamic and metabolic parameters of patients with EH and concomitant DM2, in different variants of *PPARγ2* polymorphisms, showed that patients with the *Pro/Pro* genotype of *PPARγ2* had significantly ($P < 0.01$) higher levels of blood pressure; larger LV sizes; greater IMT and PWV, with a lower EDVD degree, compared to the *Pro/Ala* and *Ala/Ala* genotypes [Table 5]. In addition, patients with the *Pro/Pro* genotype had significantly more pronounced dyslipidemia ($P < 0.01$) and IR ($P < 0.001$)

Table 5: Comparative evaluation of hemodynamic and metabolic parameters in patients of the main group depending on genotypes of *PPARγ2*

Indices	Main group (*n* = 320)		
	Pro/Pro	***Pro/Ala***	***Ala/Ala***
SBP, mmHg	172.372 ± 0.259	165.775 ± 0.351*	165.714 ± 1.017*
DBP, mmHg	101.599 ± 0.196	99.338 ± 0.232*	100.001 ± 1113
EDD LV, cm	5.024 ± 0.026	4.878 ± 0.038*	4.856 ± 0.084
ESD LV, cm	3.316 ± 0.024	3.198 ± 0.034*	3.149 ± 0.072
MMI LV, g/m	142.794 ± 2.551	136.553 ± 2.983	139.933 ± 7.664
E/A	0.924 ± 0.013	0.915 ± 0.027	0.943 ± 0.158
E/e	6.348 ± 0.097	6.108 ± 0.193	6.422 ± 0.866
IMT, mm	0.951 ± 0.006	0.900 ± 0.011*	0.849 ± 0.035*
PWV of the CA, m/c	8.910 ± 0.075	8.592 ± 0.122*	8.301 ± 0.301
PWV of the AA, m/c	9.020 ± 0.086	8.874 ± 0.146	7.779 ± 0.461*º
EDVD, %	6.155 ± 0.056	7.017 ± 0.079*	6.959 ± 0.241*
blood glucose, mmol/L	7.190 ± 0.022	6.968 ± 0.029*	6.643 ± 0.057*
HbA1c, %	7.103 ± 0.013	6.939 ± 0.058*	6.929 ± 0.042*
insulin, mcU/mL	25.182 ± 0.255	21.906 ± 1.526	22.814 ± 1.735
HOMA-IR	8.039 ± 0.083	6.767 ± 0.156*	6.722 ± 0.484*

*$P < 0.05$ *vs.* the *Pro/Pro* genotypes; º$P < 0.05$ *vs.* the *Pro/Ala* genotypes. SBP: systolic blood pressure; DBP: diastolic blood pressure; EDD LV: end-diastolic diameter of left ventricle; ESD LV: end-systolic diameter of left ventricle; MMI LV: myocardial mass index of left ventricle; E/A: ratio of the maximum velocity of early and late left ventricle filling; E/e: ratio of peak e and E on the mitral valve in the spectral and tissue Doppler; IMT: intima media thickness; PVW CA: pulse wave velocity by the carotid artery; PVW AA: pulse wave velocity by the abdominal aortic; EDVD: endothelium dependent vasodilation; HOMA-IR: homeostasis model assessment index

Table 6: Structural and functional state of the heart and vessels in the main group of patients depending on *PPARγ2* genotypes

Indices	Main group (*n* = 320)	
	***Pro/Pro* (*n* = 242)**	***Pro/Ala* + *Ala/Ala* (*n* = 78)**
EDD LV, cm	5.024 ± 0.026	4.876 ± 0.035*
ESD LV, cm	3.316 ± 0.024	3.194 ± 0.032*
MMI LV, g/m	142.794 ± 2.551	133.215 ± 2.799*
E/A	0.924 ± 0.013	0.917 ± 0.028
E/e	6.348 ± 0.097	6.136 ± 0.190
IMT, mm	0.951 ± 0.006	0.895 ± 0.011*
PWV of the CA, m/c	8.910 ± 0.075	8.566 ± 0.114*
PWV of the AA, m/c	9.020 ± 0.086	8.776 ± 0.143
EDVD, %	6.155 ± 0.056	7.012 ± 0.075*

*$P < 0.05$ *vs.* the *Pro/Pro* genotypes. EDD LV: end-diastolic diameter of left ventricle; ESD LV: end-systolic diameter of left ventricle; MMI LV: myocardial mass index of left ventricle; E/A: ratio of the maximum velocity of early and late left ventricle filling; E/e: ratio of peak e and E on the mitral valve in the spectral and tissue Doppler; IMT: intima media thickness; PVW CA: pulse wave velocity by the carotid artery; PVW AA: pulse wave velocity by the abdominal aortic; EDVD: endothelium dependent vasodilation

than patients with other *PPARγ2* genotypes.

However, the only significant difference in indicator levels, between the *Ala/Ala* and *Pro/Ala* genotypes was found in the PWV of the AA ($P < 0.05$). Given the fact that the *Pro/Ala* and *Ala/Ala* genotypes were significantly different from the *Pro/Pro* genotype, with the former genotypes collectively presenting less severe disorders of hemodynamic and metabolic indicators, but only differing from each other with respect to the PWV of the AA, and given the small percentage of patients with the homozygous *Ala/Ala* genotype, in the subsequent step, patients with the *Ala/Ala* and *Pro/Ala* genotypes were merged into a single group, namely the *Pro12Ala/Ala12Ala* genotype.

Analysis of the differences of indicators in the structural and functional state of the heart showed that patients with the *Pro12Ala/Ala12Ala* genotype had significantly smaller MMILV ($P < 0.05$) and LV sizes ($P < 0.01$) than patients with the *Pro/Pro* genotype [Table 6].

Considering previous data that *PPARγ2* affects gene expression in epithelial cells, vascular endothelium and macrophages, analysis of the state of blood vessels in different *PPARγ2* genotypes was conducted [Table 6]. Analyzing the major vessels in patients with EH and concomitant DM2 showed that IMT in patients with the *Pro12Ala/Ala12Ala* genotype was significantly less ($P < 0.001$) than in the *Pro/Pro* genotype. A significant difference ($P < 0.05$) was found in the PWV values of the CA depending on the *PPARγ2* genotype. It was also established that in the main group of patients with the *Pro/Pro* genotype, the EDVD was significantly lower ($P < 0.001$) than in the *Pro12Ala/Ala12Ala* genotype. Established features of the differences of indicators in *PPARγ2* genotypes confirm the association of *PPARγ2* polymorphisms with the severity of endothelial dysfunction and vascular remodeling in patients with comorbidity of EH and DM2.

DISCUSSION

Changes in echocardiographic parameters depending on genetic polymorphisms of the *AGTR1* gene can be regarded as a result of varying activation of AT1 receptors, leading to differential expression and proliferation of cardiomyocytes and myocardium remodeling.[14,15]

The involvement of polymorphisms of the *AGTR1* gene in the development and progression of atherosclerotic processes was demonstrated by significantly lower levels of anti-atherogenic high density lipoprotein cholesterol and significantly higher levels of glucose, HbA1c, insulin and HOMA-IR in patients with the *A/C + C/C* genotype compared to the *A/A* genotype. More pronounced IR in the *A/C + C/C* genotype can be explained by common mechanisms of hypertension and IR, including activation of the renin-angiotensin-aldosterone system, which affects the sensitivity of tissues to insulin and compensatory hyperinsulinemia.

The differences in blood pressure with respect to *PPARγ2* polymorphisms can be explained by the fact that the activity of *PPARγ2* receptors also depends on the production of proinflammatory and hypertensive cytokines by adipose tissue, which leads to hypertension.

The influence of *PPARγ2* polymorphisms in heart remodeling can be explained by the fact that *PPARγ2* act as modulators of gene expression in many tissues, including smooth muscle, thus the alteration of their activity due to polymorphisms contributes to the development and progression of cardiovascular disease.[16-20]

More pronounced metabolic disturbances in the *Pro/Pro* genotype of *PPARγ2* can be explained by the fact that *PPARγ2* control adipogenesis (including the production of free fatty acids, elevated levels of which are the cause of IR), and activity of *PPARγ2* affects production and circulation of lipoproteins and, as a consequence, the severity of atherosclerotic processes.

The modulating effect of polymorphisms of the genetic markers *AGTR1* and *PPARγ2* on the severity of cardiovascular remodeling in patients with comorbidity of EH and DM2 was, therefore, established.

In conclusion, polymorphisms of the genetic markers *AGTR1* and *PPARγ2* was associated with the development of comorbidity of EH and DM2. The *A/C* and *C/C* genotypes of the polymorphic marker *A1166C* of the *AGTR1* gene were characterized by significantly higher blood pressure and more pronounced cardiovascular remodeling compared to the *A/A* genotype. Patients with the *Pro/Pro* genotype of the *Pro12Ala* polymorphism of *PPARγ2* had more severe hemodynamic and metabolic disorders.

Authors' contributions

A. Shalimova contributed solely to this paper.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

Each patient was informed the study and gave their consent.

Ethics approval

The study protocol was supported by the Ethics Committee of the Kharkiv National Medical University.

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