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СЕРДЕЧНО-СОСУДИСТОЕ РЕМОДЕЛИРОВАНИЕ И МЕТАБОЛИЧЕСКИЕ НАРУШЕНИЯ У ПАЦИЕНТОВ С КОМОРБИДНОСТЬЮ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНИ И САХАРНОГО ДИАБЕТА 2 ТИПА В ЗАВИСИМОСТИ ОТ ПОЛИМОРФИЗМА PPARγ2

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CARDIOVASCULAR REMODELING AND METABOLIC DISORDERS IN PATIENTS WITH COMORBIDITY OF ESSENTIAL HYPERTENSION AND TYPE 2 DIABETES DEPENDING ON GENETIC POLYMORPHISM PPARγ2

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АННОТАЦИЯ

Цель работы: изучить Pro12Ala PPARγ2 полиморфизм и его связь с выраженностью сердечно-сосудистого ремоделирования и метаболических нарушений при коморбидности гипертонической болезни (ГБ) и сахарного диабета 2 типа (СД 2т) в украинской популяции.

Основная группа состояла из 287 пациентов с ГБ и СД 2т. Группа сравнения состояла из 68 пациентов с ГБ без СД 2т. Контрольная группа состояла из 25 практически здоровых лиц.

Было установлено, что во всех исследуемых группах преобладали пациенты с аллелем Pro при отсутствии достоверных различий между группами. Пациенты с Pro12Ala/Ala12Ala генотипом имели достоверно более низкие значения толщины интимы-медиа и скорости распространения пульсовой волны в сонной артерии, более низкие уровни малонового диальдегида и диеновых конъюгатов, а также достоверно более высокую степень эндотелий-зависимой вазодилатации, более высокие уровни супероксиддисмутазы и каталазы, чем пациенты с генотипом Pro/Pro. Установлено, что у пациентов с генотипом Pro12Ala/Ala12Ala имели место менее выраженные метаболические расстройства.

Выводы: генетический полиморфизм PPARγ2 влияет на выраженность ремоделирования сердца и атеросклеротических процессов в сосудах при коморбидности ГБ и СД 2т. Pro12Ala/Ala12Ala генотип можно рассматривать как протективный полиморфизм при указанной коморбидности.

ABSTRACT

The aim of the study: to investigate Pro12Ala PPARγ2 polymorphism and its association with the severity of vascular remodeling and metabolic disorders in comorbidity of essential hypertension (EH) and type 2 diabetes (DM2) in Ukrainian population.

The main group of our study consisted of 287 patients with EH in combination with DM2. The group of comparison consisted of 68 patients with EH without DM2. The control group consisted of 25 healthy individuals.

It was determined that in all study groups the dominating factor belonged to the patients with Pro allele in the absence of significant differences between the groups. The patients with Pro12Ala/Ala12Ala genotype have significantly lower values of intima-media thickness and pulse wave velocity in the carotid artery, lower levels of malondialdehyde and diene conjugates and significantly higher degree of endothelium-dependent vasodilation, higher levels of superoxide dismutase and catalase than in genotype Pro/Pro. It was determined that metabolic disorders were less pronounced in patients with genotype Pro12Ala/Ala12Ala.

Conclusions: The genetic polymorphism PPARγ2 affected the severity of heart remodeling and vascular atherosclerotic processes with comorbidity of EH and DM2. Pro12Ala/Ala12Ala genotype can be considered as a protective polymorphism at specified comorbidity.

Ключевые слова: гипертоническая болезнь, сахарный диабет 2 типа, сердечно-сосудистое ремоделирование, метаболические нарушения, генетический полиморфизм PPARγ2.

Keywords: essential hypertension, type 2 diabetes, cardiovascular remodeling, metabolic disorders, PPARγ2 genetic polymorphism.

Introduction. Essential hypertension (EH), type 2 diabetes (DM2) and obesity are three of the most common non-infectious diseases in the world. Insulin resistance (IR) is one of the pathophysiological mechanisms that affects the development and course of comorbidity EH, DM2 and obesity [4, 7, 10].

It has been found that normal insulin sensitivity largely depends on the functional activity of peroxisome proliferator-activating receptor (PPAR) [2, 3, 5, 9]. For the recent years the scientists have been paying much attention to research of PPAR polymorphism – transcription factors that control the activity of many genes, regulate lipid and carbohydrate metabolism [1, 6, 8, 11].

The aim of this study was to investigate Pro12Ala PPARγ2 polymorphism and its association with the severity of vascular remodeling and metabolic disorders in comorbidity of EH and DM2 in Ukrainian population.

Clinical characteristics of patients and research methods. We examined 287 patients of Ukrainian population, aged from 45 to 60 years old with EH stage II grade 2 and DM2 moderate, subcompensated (the main group); 68 patients with EH stage II grade 2 without DM2 (the comparison group). The control group consisted of 25 healthy individuals with no EH and DM2, as they were excluded on the basis of the complex clinical and instrumental examinations.

Inclusion criteria to the study: EH stage II grade 2; type 2 diabetes moderate, subcompensated; CHF I–II FC, normal weight (body mass index (BMI) – 18–24,9) , overweight (BMI – 25–29.9), obesity I degree (BMI – 30–34,9), abdominal obesity (criteria IDF, 2005), normal glomerular filtration rate (GFR), normocreatininemia absence of proteinuria (admissible only microalbuminuria), age patient 45–60 years; established disease duration EH – 12,8 years, type 2 diabetes – 3–7 years; irregular antihypertensive drugs.

Exclusion criteria from the study: presence of comorbidity in patients with EH and DM2 (acute coronary syndrome, myocardial infarction, arrhythmias and conduction, rheumatic heart disease, systemic connective tissue diseases, cancer diseases, symptomatic hypertension, thyroid disease, acute inflammation), type 1 diabetes; EH stage III, grade 3, CHF III–IV FC, type 2 diabetes in mild and severe forms of compensation and decompensation phases; insulin therapy in patients with type 2 diabetes; obesity II–III degrees, reduced GFR, proteinuria; age of the patients less than 45 and more than 60 years; echonegativity; refusal of patients from the study.

Working with patients, involved in the study, using standard biochemical methods we defined glucose concentration of venous blood glucose, glycosylated hemoglobin (HbA1c), insulin, total cholesterol, triglycerides, high density cholesterol (HDL cholesterol) and low density cholesterol (LDL cholesterol). IR was assessed by HOMA index (HOMA-IR). Levels of oxidative stress indicators - malondialdehyde (MDA) and diene conjugates (DC), and antioxidant protection - superoxide dismutase (SOD) and catalase superoxide dismutase (SOD) and catalase were studied with spectrophotometric methods.

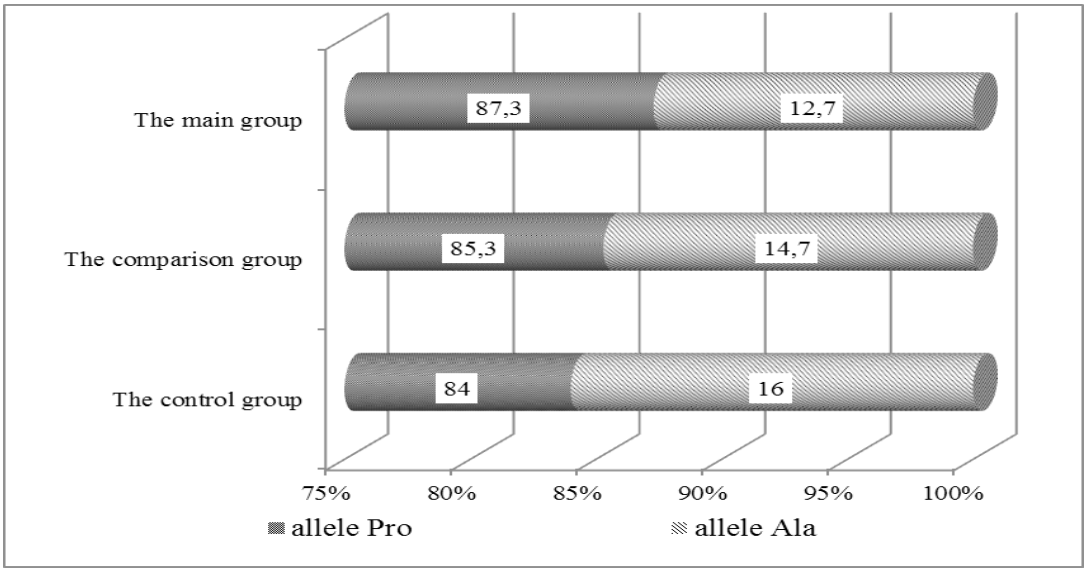
Ultrasound examinations were performed on cardiac ultrasound scanner («ULTIMA RA» firm «RADMIR», Ukraine) in one-, two-dimensional and Doppler modes with color mapping by conventional methods. For the study of endothelial function determination of the degree endothelium-dependent vasodilation (EDVD) in reactive hyperemia was conducted in all patients. Investigations were carried out broadband linear transducer 5–12 MHz Doppler color mapping with three on the left and right brachial artery in 15-minute intervals between samples by the method of Celermajer D.S. in modification Ivanova O.V. Normally, the maximum vasodilation of the brachial artery have to exceed 10% of the original diameter. Simultaneously, we measured the of 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) by the CA was determined W-Track- method (method of phase tracking, patented scanner manufacturers).

Pro12Ala polymorphism of PPARγ2 was assessed by molecular genetic method. We have identified three genotypes of PPARγ2 by Pro12Ala polymorphism (Pro/Pro, Pro/Ala and Ala/Ala). The distribution of allele frequencies corresponded to the Hardy-Weinberg law.

Statistical data processing was performed using the software package «Statistics for Windows» 6.0.

Results and their discussion.

It was determined that in all study groups the dominating factor belonged to the patients with Pro allele in the absence of significant differences between the groups (Figure 1).



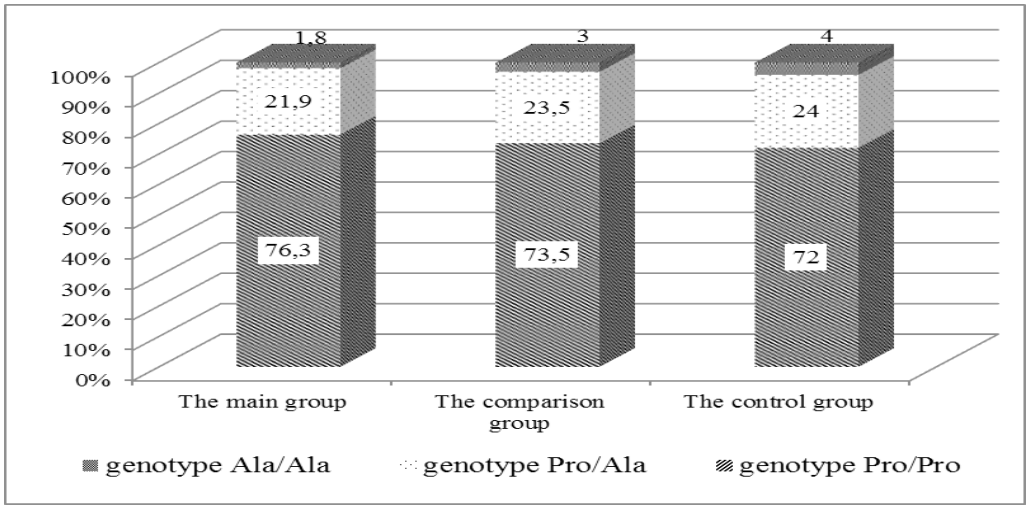


Figure 1 The distribution of PPARγ2 alleles and genotypes in the patients

According to other researchers the similar distribution of genotypes of PPARγ2 it is generally typical for European population [6, 8, 9].

The patients of main group with Pro12Ala/Ala12Ala genotype had significantly ($p<0,01$) lower values of IMT and PWV in the carotid artery and significantly ($p<0,001$) higher degree of EDVD than in genotype Pro/Pro (Figure 2).

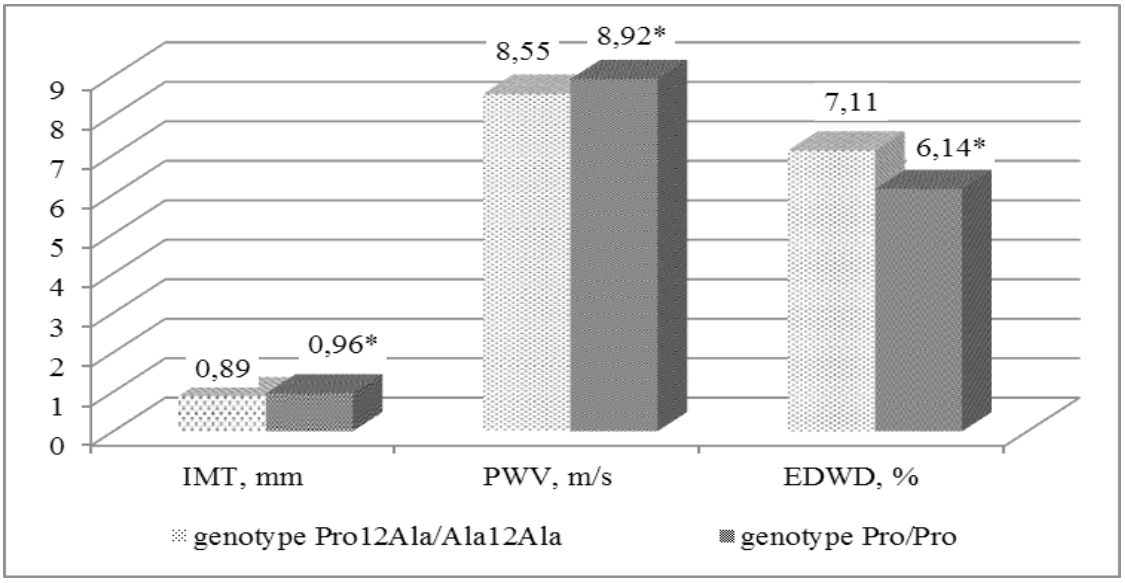


Figure 2 The indicators of vascular remodeling in the patients of main group
Note: * – statistically significant differences between genotypes Pro12Ala/Ala12Ala and Pro/Pro in the main group.

The patients with Pro12Ala/Ala12Ala genotype had significantly lower values of oxidative stress indicators - MDA and DC; and significantly higher levels of indicators of antioxidant protection - SOD and catalase than in genotype Pro/Pro (Table 1).

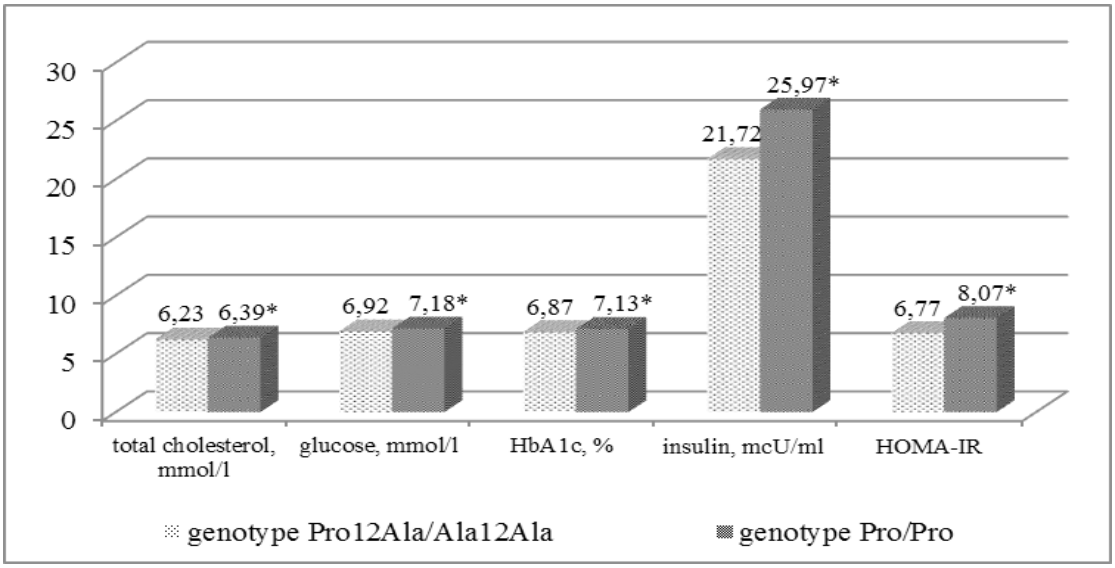
Table 1

The indicators of oxidative stress and antioxidant protection in the patients of the main group

Indices	genotype Pro12Ala/Ala12Ala	genotype Pro/Pro
MDA, nmol/l	37,41 ± 0,14	39,02 ± 0,07*
DC, nmol/l	36,75 ± 0,21	38,67 ± 0,14*
SOD, U/mg Hb min	43,08 ± 0,11	39,92 ± 0,05*
Catalase, U/mg Hb min	0,114 ± 0,001	0,110 ± 0,001*

Note: * – statistically significant differences between genotypes Pro12Ala/Ala12Ala and Pro/Pro in the main group.

It was determined that metabolic disorders were less pronounced in patients with genotype Pro12Ala/Ala12Ala, what was confirmed by lower levels of total cholesterol, glucose, HbA1c, insulin, less pronounced insulin resistance and higher levels of high-density lipoproteins ($p<0,001$) (Figure 2).



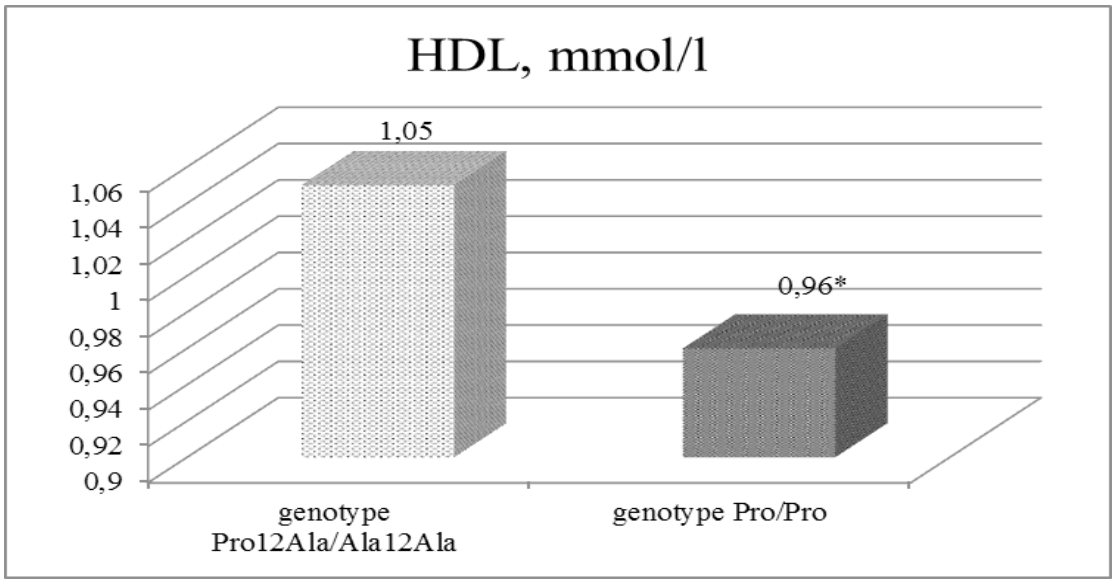


Figure 3 The severity of metabolic disorders in the patients of the main group
Note: * – statistically significant differences between genotypes Pro12Ala/Ala12Ala and Pro/Pro in the main group.

The main features for genotype Pro12Ala/Ala12Ala were significantly lower blood pressure, smaller sizes of left ventricle (LV) and myocardial mass index (MMI) LV than for Pro/Pro genotype (Figure 4).

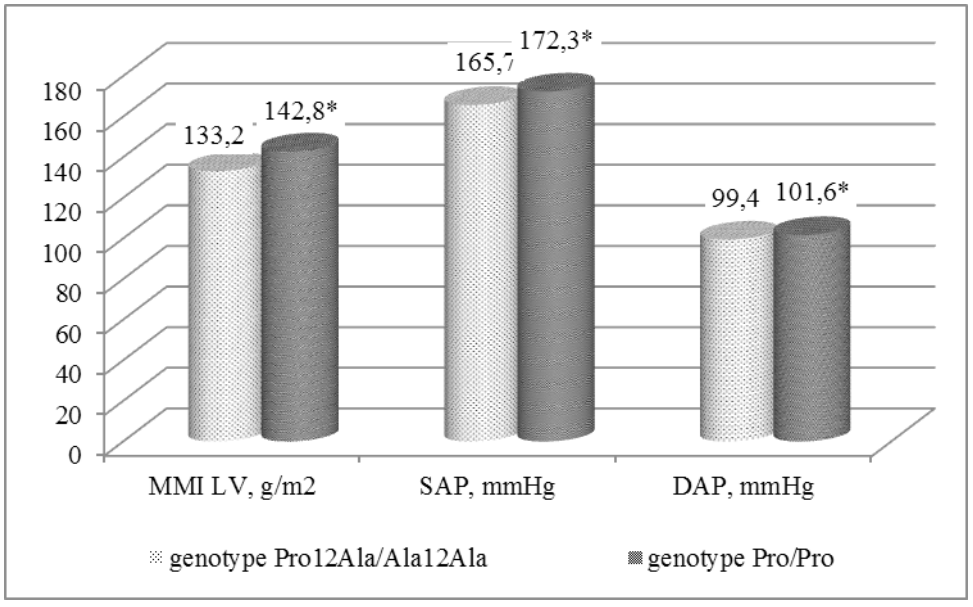


Figure 4 Hemodynamic and echocardiographic indices in the patients of the main group
Note: * – statistically significant differences between genotypes Pro12Ala/Ala12Ala and Pro/Pro in the main group.

Conclusions

1. The genetic polymorphism PPARγ2 affected the severity of heart remodeling and vascular atherosclerotic processes, the level of blood pressure with comorbidity of EH and DM2 in Ukrainian population of patients.

2. Pro12Ala/Ala12Ala genotype can be considered as a protective polymorphism at specified comorbidity.

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