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PATHOGENETIC CONNECTION OF LIPID PROFILE CHANGES WITH LEFT VENTRICLE HYPERTROPHIC MODELS DEPENDING ON GENES POLYMORPHISM' ACE (I/D), ENOS (T894G) IN PATIENTS WITH ESSENTIAL HYPERTENSION

Key words: arterial hypertension, genetic polymorphism, lipid profile, left ventricle hypertrophy.

Abstract.

Purpose. To establish the dependence of lipid profile changes in patients with essential arterial hypertension (EAH) on the type of left ventricular hypertrophy (LVH) and gene polymorphism of angiotensin-converting enzyme (ACE, I/D) and endothelial nitric oxide synthase (eNOS, T894G).

Design/approach. In a prospective study 120 patients with EAH I-III severity stages: 12,5% (15) persons with EAH I, 60,0% (72) with EAH II, 27,5% (33) with EAH III; 48,3% (58) women and 51,7% (62) men, mean age 52,91±9,24, the disease duration from 2 to 28 years; the control group - 20 healthy individuals were involved. Ventricular mass (LVM) was evaluated by Echo-KG. Plasma lipids were studied by spectrophotometer, analyzed according to the recommendations of the ESC, ESH (2009). Genes' allele polymorphic areas of ACE (I/D), eNOS (T894G) were set by PCR analysis.

Findings. High-risk groups of lipid profile changes in patients with EAH is a carriers of DD-genotype of ACE gene by increasing of low density cholesterol level and atherogenic index by 1,3 times ($p<0.05$). Genetic risk of dyslipidemia in EAH patients with unfavorable eccentric and concentric LVH and ACE and eNOS genes mutations (ID/TT, ID/TG, DD/TG haplotypes) increases by 2,57-3,86 time (OR=2,57-3,86). Combination of Wild I-allele of ACE gene and G-allele of eNOS gene (II/GG, II/TG haplotypes) is protective against development of hypercholesterolemia in patients with unfavorable patterns of LVH (OR=0,12-0,94) and makes the chances of dyslipidemia risk the lowest in the population of EAH patients ($p=0.05$).

Research limitations/implications. The study is limited by the peculiarities of laboratory and diagnostic tests.

Originality/value. The original research without a prototype provides pathogenetic data for early detection and prevention of metabolic disorders in the presence/absence of LVH in patients with EAH.

Introduction

Left ventricular hypertrophy (LVH) is one of the key manifestations of the cardiac damage, as target-organ at arterial hypertension (AH). LVH increases frequency of cardio-vascular complications (CVC) twice according to Fleming's research and works of R.B. Devereux et al [3,11] independently of the other risk factors (hypercholesterolemia, old age, high office or daily AH), increases general mortality from cardio-vascular diseases (CVD), frequency of myocardial infarction, need in revascularization. It has been proved that an increase of the LV wall thickness in patients with arterial hypertension by 1 mm is associated with an increase of death risk almost 7 times [4]. On the level with LVH dislipidemia is the factor that determines unfavourable prognosis of the patient with AH. In the latest fundamental clinical investigations (HPS, PROVE-IT, REVERSAL and others) it has been proved that normalization of the general cholesterol content (GCC) and reduction of lipoproteins cholesterol level of low density (CL LPLD) below standard meanings in persons with ischemic cardiac disease does not result in complete prevention of atherosclerosis progression and development of cardiac manifestations [1, 9, 13]. It has been also proved that genetic absence of apoprotein anoE in mice, or receptors to LPLD is accompanied by marked lipid metabolism impairments and spontaneous atherosclerosis development. However, if these changes are connected

with absence of the receptors to angiotensin II of type I (AGTR1), or with the use of their blockers, then atherosclerosis development slows down sharply in spite of hypercholesterolemia and marked systemic lipid impairments. So, not so much GCC, as activation of rennin-angiotensin-aldosterone system (RAAS), mainly with the tissue one and not circulatory, determines the development of atherosclerotic damage [10, 12]. Combination of dislipidemia, atherosclerosis and LVH makes significantly worse the course of the principle disease and patient's prognosis [1, 2, 5].

In spite of the great number of investigations, questions of the genetic susceptibility of patients with CVD to the development of dislipidemia through RAAS and myocardium remodeling as a potential target of disculatory and humoral impairments, in the support of compensatory-adjusting mechanisms of the pathogenetic defence in continuing AH remain not studied nowadays. Stratification of clinico-genetic markers, which are associated with lipid metabolism changes and geometric models of hypertrophic myocardium in patients with essential AH (EAH), with the following determination of high risk groups of dislipidemia development is also of particular interest to our mind.

Aim of the research

To establish the dependence of lipid profile changes in patients with EAH upon LVH type and gene polymorphism of angiotensin-converting enzyme (ACE, I/D) and endothelial nitric oxide synthase (eNOS, T894G).

Materials and methods

147 patients with EAH I-III stages of severity (ESH, 2009) [5, 7] took part in a prospective investigation. 120 patients with EAH I-III, who signed informative agreement of a patient for taking part in the investigation with the following blood sampling for genetic analysis underwent screening stage. Among patients there were 125% (15) of persons with EAH I, 60,0% (72) - with EAH II, 27,5% (33) - with AH III stage; 48,3% (58) were women and 51,7% (62) - men, the average age was 52,91± 9, 24 years, disease duration was from 2 till 28 years (in average 15, 73±8,02 years). Control group constituted 20 practically healthy persons of the corresponding age and gender.

Aleles of polymorfous ares I/D gene ACE and T8946 eNOS gene were studied by means of polymerase chain reaction (PCR) using amplyficator "Amply-4L" (Moscow). DNA fragments were divided by gel-electrophoresis method, visualized by means of transluminator.

Echo-KG was carried out on automated diagnostic complex SonoAce8000 SE ("Medison", Korea): in M- and B-regiments standard linear data of structural-functional condition of LV, including LV geometry were analyzed in M- and B- regimens. Miocardium mass of the LV (MMLV) was estimated according to Penn Convention, MMLV index (GMMLV) was calculated by correlation of MMLV to the body surface square in g/m^2; criterion of LVH presence, according to the European recommendations ESH, ESC (2007, 2009), was considered GMMLV in men ≥125 g/m^2, in women ≥110 g/m^2. The following geometric models f the LV myocardium were determined according to the indices of GMMLV and relative thickness of the LV walls (RTWLV): standard geometry of the LV (SG, LV), concentric remodeling of the LV (CR LV), eccentric hypertrophy of the LV (EH LV), concentric hypertrophy of the LV (CH LV). All patients also underwent complex of examinations: ECG in 12 standard leads USE of the kidneys and organs of the abdominal cavity, general clinical and biochemical analyses, consultations of ophthalmologists and neuropathologists.

Investigations of the blood plasma lipids included determination of general cholesterol (GCS), triglycerides (triacilglycerols, TG) using "Cholesterol PAP SL Mono" an "Triglycerides SL Mono" reagents ("Biopharma", France-Ukraine) and CS of lipoproteins of high, low and too low density (CS LPHD, CS LPLD, CS LPTLD) ("Biosystem" S.A., Spain), investigations were carried out on spectrophotometer ("PM", Finland), with the wave length of 500±20mm [6]. Atherogene index (GA) was calculated by A.N. Klimov's formula: GA= (GCS - CS LPHD)/CS LPHD. According to recommendations of ESC, ESH and Ukrainian association of cardiologists GCS <5,0 mmol/l, GC LPHD <3,0 mmol/l, GC LPHD in men >1,0 mmol/l, in women >1,2 mmol/l, TG <1,7 mmol/l [2,5], GA ≤2,5 were taken as normal ("having a special purpose") indices abdominal obesity was determined by means of waist dimension for men >102 cm, for women >88 cm [5, 6]. Index of body weight (BWI kg/m^2) was measured by ratio of the body mass to height, raised to square. BWI was considered according to the recommendations of National Institute of Health, USA and North-American association in obesity study, as normal - 18,5-24,9 kg/m^2, heightened mass BWI - 25-29,9 kg/m^2, obesity BWI >30 kg/m^2 [8].

Statistical processing was carried out by means of applied programmes MS® Excel® 2003™, Primer of Biostatistics® 6.05 and Statistica® 7.0 (StatSoft Inc., USA). Indices truth for independent selections were calculated using unpaired t-criterion

Student (division according to Kolmogarov-Smirnov and W-criterion Shapiro-Wilk tests were close to normal), or U-criterion Wilcoxon-Mann-Whitney; analyses of qualitative signs - by χ^2 criterion. The difference was considered probable at p<0,05.

Results

The content of GCS, TG, CS LPHD and IA was probably higher in patients with EAH II-III stages than in patients with EAH I stage and practically healthy ones (p<0,05). CS LPHD decreased with an increase of EAH severity, but probably only in patients with EAH III stage in women and men against those with EAH I stage on 19,1% and 27,9% (p<0,05) correspondingly.

As to ACE indices of lipid profile between genotypes carries did not essentially differed, although CS LPHD and IA in carriers of D-allele excelled those in persons of the control group in 1,4-2,0 times (p<0,05), and in patients with DD-genotype given indices were higher than in homozygous patients with I-allele in 1,3 times (p<0,05). In T-allele carries of eNOS gene IA exceeded the same in the group of control in 1,7 and 1,96 times (p<0,05) correspondingly.

Lipid profile depending on geometric myocardium models of the left ventricle in patients with EAH is given in table 1. Insignificant reduction of CS LPHD were observed both in men and women with CG LV 1,3 and 1,2 times (p=0, 054-0,056) in case of CS LHPD in IA increase in patients with hypertrophic geometric models (EH LV and CH LV) 1,4 times (p=0,036-0,039) and 1,5 and 1,6 times (p< 0,01), correspondingly. IA in patients with CH LV exceeded the same in patients with CR LV 1,2 times (p=0,05).

Analysis of indices changes of lipid metabolism with regard for haplotypes of genes ACE (I/D) and eNOS (T894G) (table 2) is the evidence of probably greater IA in carriers of DD/TG and DD/GG-haplotypes than in those with II/GG-haplotype by 18,7% (p≤0,05), respectively. Reliable distinctions were not revealed as to other indices. Essential changes were not observed too (p>0,05) at lipid profile analysis depending on geometry of the LV myocardium according to haplotypes genes ACE (I/D) and eNOS (T894G).

Epidemiological analysis of the indices of an increase of absolute and relative risks of dislipidemia onset in presence of unfavourable hypertrophic models of the LV myocardium depending on nine haplotypes or their combinations with calculation of the ratio of risks, chances and corresponding confidence intervals is given in table 3. Carrier state of mutant D-allele gene ACE and T-allele gene eNOS in haplotype (ID/TT, ID/TG, DD/TG) is unfavourable factor and increases the risk of dislipidemia onset in EAH patients with EH LV, or CH LV 2,57, 4,21 and 3,86 times, correspondingly. Instead of, the presence of II-genotype of gene ACE in haplotype, with regard for genotypes of gene eNOS, decreases the given risk to the probability of 0,32-0,95 time (OR=0,12-1,17), but combination of wild homozygous I-allele of gene ACE and G-allele of eNOS gene (II/GG haplotype) is projective as to the hypercholesterolemia development in patients with unfavourable patterns of LVH (OR=0,12) and makes risk chances of dislipidemia the lowest in the population of patients with EAH (p=0,05) under study. A reliable dependence on MM LV with GCS

Table 1

Lipid profile in patients with EAH depending on geometric models of the left ventricle

Geometric model LV		NG LV, n=10 (8,3%)	CR LV, n=15 (12,8%)	EH LV, n=38 (31,7%)	CH LV, n=57 (47,5%)
GCS, mmol/l		5,05±0,52	5,81±0,87	6,04±0,56	6,07±0,63
CS LPHD, mmol/l	m	1,28±0,14	1,20±0,11	1,08±0,23	1,01±0,15 p=0,054
	w	1,40±0,15	1,33±0,22	1,24±0,19	1,20±0,13 p=0,056
CS LPLD, mmol/l		2,65±0,25	3,46±0,58	3,80±0,61 p=0,039	3,75±0,52 p=0,036
TG, mmol/l		1,36±0,24	1,64±0,15	1,77±0,18 p=0,053	1,72±0,21
IA, cond.un.		2,75±0,29	3,61±0,47 p=0,052	4,20±0,42 p<0,01	4,49±0,33 p<0,01 p_1=0,05

Notes: 1. GCS – general cholesterole; CS LPHD/LPLD – lipoproteins cholesterole of high/low density; IA – atherogenicity index; M – men; W – women; NGLV - normal geometry of the left ventricle (LV); CRLV – concentric remodeling of the LV; EHLV – eccentric hypertrophy of the LV; CHLV – concentric remodeling of the LV. 2. p – probability of indices differences relatively to NGLV; p1 – probability of differences indices relatively to CRLV; p2 – probability of differences indices relatively to EHLV

Table 2

Lipid profile in EAH patient depending on haplotypes of ACE (ID) genes and eNOS (T894G)

Lipid indices	Genotypes' combination of ACE (I/D) and eNOS (T894G)		
	II/TT, n=2	**II/TG, n=13**	**II/GG, n=9**
GCS, mmol/l	5,58±0,65	5,31±0,43	5,37±0,52
CV LPHD, mmol/l	1,20±0,24	1,23±0,25	1,26±0,12
CS LPHD, mmol/l	3,44±0,43	3,25±0,37	3,26±0,50
TG, mmol/l	1,58±0,32	1,66±0,28	1,67±0,22
IA, cond.un.	3,61±0,56	3,50±0,71	3,21±0,24 DD/TG DD/GG
	ID/TT, n=7 (%)	ID/TG, n=31 (%)	ID/GG, n=24
GCS, mmol/l	5,86±0,90	5,59±0,69	5,65±0,45
CS LPHD, mmol/l	1,17±0,19	1,21±0,13	1,23±0,10
CS LPHD, mmol/l	3,73±0,47	3,55±0,38	3,56±0,57
TG, mmol/l	1,65±0,30	1,64±0,21	1,66±0,20
IA, cond.un.	4,0±0,45	3,62±0,55	3,59±0,78
	DD/TT, n=0	DD/TG, n=20	DD/GG, n=14
GCS, mmol/l	–	5,74±0,42	5,68±0,89
CS LPHD, mmol/l	–	1,18±0,15	1,20±0,10
CS LPLD, mmol/l	–	3,67±0,44	3,69±0,55
TG, mmol/l	–	1,63±0,29	1,62±0,19
IA, cond. un.	–	3,86±0,30	3,78±0,32

Notes: 1. Commentary of abbreviations are corresponding to Table 1. 2. Probability of indices' differences relatively to certain haplotype is raised to the degree ($p \leq 0,05$)

Table 3

Genotype combinations of I/D polymorphism of gene ACE and T849G of eNOS gene as risk factors of dislipidemia onset in EAH patients with hypertrophic models (eccentric/ concentric hypertrophy of the left ventricle)

№	Potential risk factor	ARI / ARR	RRI / RRR	RelR	RR	OR	95 CI RR / 95 CI OR	p
1.	Presence of II/GG	0,48	0,68	0,32	0,59	0,12	0,21-4,05 / 0,28-5,12	0,05
2.	Presence of II/TG, II/GG	0,15	0,22	0,78	0,85	0,94	0,53-4,33 / 0,39-9,55	0,05
3.	Presence of II/TT	0,03	0,05	0,95	1,11	1,17	0,17-7,13 / 0,07-18,35	>0,05
4	Presence of II/GG, ID/GG	0,12	0,18	0,82	1,41	1,72	0,51-3,95 / 0,38-7,85	>0,05
5	Presence of ID/TT	-0,16	-0,22	1,22	1,35	2,57	0,33-5,95/ 0,11-12,0	>0,05
6	Presence of ID/TG	-0,23	-0,34	1,23	1,62	3,21	0,42-11,09 / 0,22-11,5	0,08
7	Presence of ID/GG	-0,01	-0,01	1,01	0,96	1,04	0,31-3,02 / 0,19-4,82	>0,05
8	Presence of DD/TG	-0,20	-0,28	1,29	1,83	3,86	0,66-7,64/ 0,35-18,98	>0,05
9	Presence of DD/GG	-0,08	-0,12	1,12	0,99	1,57	0,29-3,09/ 0,19-4,09	>0,05

Note: ARI (absolute risk increase) / ARR (absolute risk reduction) – increase / decrease of absolute risk; RRI (relative risk increase) / RRR (relative risk reduction) – increase / decrease of relative risk; Re1R (relative risk) – relative risk

and IA, but only in patients of high and very high cardio-vascular risk with a damage of target organs and evident complications (r=0,51-0,60, p≤0,042-0,005) was revealed when analyzing correlative relations. In patients with EAH III MM LV was also associated with the level of CS LP HD (r=0,47; p=0,035) and BWY (r=0,49, p=0,028). The evidence of the direct reliable relation of MM LV in carriers of D-allele MT with BWY (r=0,39-0,41; p=0,044-0,039), in carriers of DD-genotype - with GCS (r=0,60; p=0,005), CS LPTLD and CS LPHD (r=0,42-0,53; p=0,039-0,017) correspondingly was established depending on allele state of ACE gene. In T-allele carriers gene eNOS MM LV correlated reliably only with BWY (r=0,32-0,39; p=0,044-0,02), but in GG-genotype carriers with CS LPHD (r=0,75; p=0,021) with the reverse dependence upon CS LPHD (r=0,81; p=0,011).

Thus, to our mind, the data obtained are the results of realizations of genetically determinated clinical phenotype EAH that is accompanied by structural-functional change of the LV myocardium and associated changes of lipid metabolism that gives the possibility to determine groups of dislipidemia risk depending upon haplotype and geometric model of LVH.

Conclusions

1. Carriers of DD-genotype of gene ACE according to the content increase of CS LPHD and atherogenecity index 1,3 times (p<0,05) are the risk groups of lipid profile disorder in patients with EAH.

2. Genetically stipulated risk of dislipidemia onset in patients with EAH in presence of unfavourable eccentric and concentric LVH and mutations of ACE genes (homozygous, or heterozygous presence of D-allele in haplotype) and eNOS (ID/TT, ID/TG, DD/TD haplotypes) increase 2,57-3,86 times. Combination of the wild I-allele of ACE gene and G-allele of e NOS gene (II/GG, II/TG haplotypes is projective as to hypercholesterolemia development in patients with unfavourable LVH patterns (OR=0,12-0,94) and makes chances of dislipidemia risk the lowest in population of patients with EAH under study.

3. MMLV probably correlates: with GCS and IA in patients with EAH of the II and III st., with BWY in patients with EAH III st., D-allele carriers of ACE gene and T-allele of eNOS gene, with GCS, CS LPTDD and CS LPLD in patients with DD-genotype and CS LPLD and CS LPHD in patients with GG-genotype of eNOS gene.

Perspectives of further research lie in studying the condition of vascular arterial bloodstream in patients with EAH depending on polymorphism of the chosen genes, severity of hypertension and geometry to the left ventricle miocardium.

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ПАТОГЕНЕТИЧНИЙ ЗВ'ЯЗОК ЗМІН ЛІПІДНОГО ПРОФІЛЮ І МОДЕЛЕЙ ГІПЕРТРОФОВАНОГО МІОКАРДА ЛІВОГО ШЛУНОЧКА ЗАЛЕЖНО ВІД ПОЛІМОРФІЗМУ ГЕНІВ ACE (I/D), ENOS (T894G) У ХВОРИХ НА ЕСЕНЦІАЛЬНУ ГІПЕРТЕНЗІЮ

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Мета дослідження. Встановити залежність змін ліпідного профілю у хворих на есенційну артеріальну гіпертензію (ЕАГ) від виду гіпертрофії лівого шлуночка (ГЛШ) та поліморфізму генів ангіотензин-перетворювального ферменту (ACE, I/D) і ендотеліальної оксиду азоту синтази (eNOS, T894G).

Дизайн/підхід. У проспективному дослідженні взяло участь 120 хворих на ЕАГ I-III стадій тяжкості: 12,5% (15) осіб із ЕАГ I, 60,0% (72) із ЕАГ II, 27,5% (33) із ЕАГ III ст.; 48,3% (58) жінок і 51,7% (62) чоловіків, середній вік 52,91±9,24 року, тривалість захворювання від 2 до 28 років; контрольна група - 20 практично здорових осіб. Масу міокарда ЛШ (ММЛШ) оцінювали методом Ехо-КГ. Ліпіди плазми досліджували на спектрофотометрі, аналізували відповідно до рекомендацій ESC, ESH (2009). Алелі поліморфних ділянок генів ACE (I/D), eNOS (T894G) - за допомогою ПЛР аналізу.

Результати дослідження. Групами ризику порушення ліпідного профілю у хворих на ЕАГ є носії DD-генотипу гена ACE за зростанням вмісту холестеролу ліпопротеїдів низької густини та індексу атерогенності у 1,3 раза (p<0,05). Генетично зумовлений ризик появи дисліпідемій у хворих на ЕАГ за наявності несприятливих ексцентричної та концентричної ГЛШ і мутації генів ACE та eNOS (ID/TT, ID/TG, DD/TG гаплотипи) зростає у 2,57-3,86 раза (OR=2,57-3,86). Комбінація дикої I-алелі гена ACE та G-алелі гена eNOS (II/GG, II/TG гаплотипи) є протективним щодо розвитку гіперхолестеролемії у хворих із несприятливими патернами ГЛШ (OR=0,12-0,94) і робить шанси ризику дисліпідемій найнижчими в обстежуваній популяції хворих на ЕАГ (p=0,05).

Обмеження дослідження/наслідки. Обмеження зумовлені особливостями проведення лабораторно-діагностичних досліджень.

Оригінальність / значення. Оригінальне дослідження без прототипу, надає патогенетичні дані для ранньої діагностики та профілактики метаболічних порушень за наявності/відсутності ГЛШ у хворих на ЕАГ.

Ключові слова: артеріальна гіпертензія, генетичний поліморфізм, ліпідний профіль, гіпертрофія лівого шлуночка.

ПАТОГЕНЕТИЧЕСКАЯ СВЯЗЬ ИЗМЕНЕНИЙ ЛИПИДНОГО ПРОФИЛЯ И МОДЕЛЕЙ ГИПЕРТРОФИРОВАННОГО МИОКАРДА ЛЕВОГО ЖЕЛУДОЧКА В ЗАВИСИМОСТИ ОТ ПОЛИМОРФИЗМА ГЕНОВ ACE (I/D), ENOS (T894G) У БОЛЬНЫХ ЭССЕНЦИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

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Цель исследования. Исследовать особенности изменений липидного профиля у больных эссенциальной артериальной гипертензией (ЭАГ) в зависимости от вида гипертрофии левого желудочка (ГЛЖ) и полиморфизма генов ангиотензин-превращающего фермента (ACE, I/D) и эндотелиальной окиси азота синтазы (eNOS, T894G).

Дизайн/подход. В проспективном исследовании приняли участие 120 больных ЭАГ I-III стадий тяжести, среди них у 12,5% (15) - ЭАГ I, у 60,0% (72) - ЭАГ II, у 27,5% (33) - ЭАГ III ст.; 48,3% (58) женщин и 51,7% (62) мужчин, средний возраст 52,91±9,24 года, длительность заболевания от 2 до 28 лет; контрольная группа - 20 практически здоровых лиц. Массу миокарда ЛЖ (ММЛЖ) определяли методом Эхо-КГ. Липидный профиль плазмы исследовали на спектрофотометре, анализировали соответственно рекоммендаций ESC, ESH (2009). Аллели полиморфных участков генов ACE (I/D), eNOS (T894G) - с помощью ПЦР анализа.

Результаты исследования. Среди больных ЭАГ группами риска изменений липидного профиля с увеличением содержания холестерина липопротеидов низкой плотности и индекса атерогенности в 1,3 раза (p <0,05) являются носители DD-генотипа гена ACE. Генетически обусловленный риск появления дислипидемий у больных ЭАГ при наличии неблагоприятных эксцентричной и концентрической ГЛЖ и мутации генов ACE и eNOS (ID /TT, ID/TG, DD/TG гаплотипы) возрастает в 2,57-3,86 раза (OR = 2,57-3,86). Комбинация дикой I-аллели гена ACE и G-аллели гена eNOS (II/GG, II/TG гаплотипы) предупреждает развитие гиперхолестеролемии у больных с неблагоприятными паттернами ГЛЖ (OR = 0,12-0,94) и делает шансы риска дислипидемий наиболее низкими в обследуемой популяции больных ЭАГ (p=0,05).

Ограничения исследования/ последствия. Ограничения обусловлены особенностями лабораторно-диагностических исследований.

Оригинальность/значение. Оригинальное исследование без прототипа предоставляет патогенетические данные для ранней диагностики и профилактики метаболических нарушений при наличии / отсутствии ГЛЖ у больных ЭАГ.

Ключевые слова: артериальная гипертензия, генетический полиморфизм, липидный профиль, гипертрофия левого желудочка.

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