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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

INTEGRIN GENE POLYMORPHISM AND RISK OF ISCHEMİC HEART DISEASE IN PATIENTS WITH ARTERIAL HYPERTENSION

Specialty: 3218.01 – Cardiology

Field of science: Medicine

Applicant: **Vafa Balabay Nazirova**

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The work was performed at the Department of Cardiology of Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev, Special Treatment Health Complex and Shafa Therapeutic Diagnostic Center

Scientific supervisor: Doctor of Medical Sciences, Professor
Faig Ali-Mukhtar Guliyev

Official opponents: Doctor of Medical Sciences, Professor
Adil Bakhshali Bakhshaliyev

Doctor of Medical Sciences
Elman Zaur Alakbarov

Doctor of Philosophy
Tofig Gudrat Sadigov

Dissertation Council ED 2.27 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at Azerbaijan Medical University

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GENERAL CHARACTERISTICS OF THE WORK

Relevance and development rate of the topic: In modern medical science, arterial hypertension (AH) is considered as a cascade of metabolic, hemodynamic and neurohormonal factors. The damage to the blood vessels is primarily caused by this cascade, and its most severe manifestation, myocardial ischemia, leads to disability and death.[1]

As in the whole world, in Azerbaijan, arterial hypertension and cardiovascular diseases (CVD) are among the most pressing in healthcare and hold siginificant socioeconomic importance.[2]

At the beginning of the 21st century, medicine entered a new era, the main line of which is the availability of genetic technologies necessary to understand the structural and functional organization of the human genome in normal and pathological conditions.

An important role in this process is played by the state of hemostasis. Under normal conditions, there is a balance between the coagulation and anticoagulation systems in the blood. When this balance is disrupted, the enzyme thrombin, produced in the liver, is released. Thrombin has the ability to break down fibrinogen, a protein that circulates in the blood.[3]

Fibrinogen, which plays a key role in the development of thromboembolism and can lead to the development of cardiovascular diseases, is also a predictor of myocardial ischemia and arterial hypertension.

Genome-Wide Association Studies (GWAS) have identified more than 100 single nucleotide polymorphisms (SNPs) associated with arterial pressure (AP) phenotypes. Disruption of the nucleotide sequence leads to the formation of a altered (mutant) genotype.[4]

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[1] Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020;16(4):223-237

[2] Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D.et al. International Society of Hypertension Global Hypertension Practice Guidelines // Hypertension. 2020; 75:1334–1357

[3] Yang S.H., Du Y., Zhang Y. et al. Serum fibrinogen and cardiovascular events in Chinese patients with type 2 diabetes and stable coronary artery disease: a prospective observational study. BMJ.2017; Vol.7(6): e015041.DOI: 10.1136/ bmjopen-2016-015041

[4] Чернявина, А.И., Суровцева, М.В. Вклад полиморфизма генов сердечно-сосудистого риска в развитие артериального ремоделирования в зависимости

A group of genes, candidate genes, responsible for the development of cardiovascular diseases, including arterial hypertension, play an important role in the pathogenesis of the disease. Identification of genes associated with arterial hypertension will provide a mechanism for classifying hypertensive phenotypes and allow the development of diagnostic markers for individual patients and families at risk of complications such as ischemic heart disease (IHD), myocardial infarction, and stroke. Advances in the field of cardiogenetics make it possible to identify candidate genes responsible for the development of cardiometabolic disorders. Arterial pressure is the leading hereditary risk factor for cardiovascular disease worldwide. Although risk factors for vascular phenotypes are associated with, for example, smoking, sedentary lifestyle, and poor diet, they are also associated with genetic background. Measurement of genetic markers is convenient for screening high-risk individuals at a very early age. As with most polygenic diseases, ischemic heart disease is caused by several common genes, and genetic predisposition is transmitted by multiple genes.[5]

It was determined that ITGA2 C807T allele is present in 72.1% of patients with acute coronary syndrome and coexists with increased platelet aggregation. Mutations in the ITGA2 and ITGB3 genes have been found to be associated with the risk of early myocardial infarction, embolism, and thrombosis. It has been demonstrated that all exons and introns of the ITGB3 gene contain multiple polymorphic sites, one of which has been identified to be associated with cardiovascular disease. It has been reported that the polymorphism of codon 33 of exon 2 of ITGB3 gene corresponds to polymorphism of amino acid (leucine/proline at position 33). This SNP has been reported to be a risk factor for many diseases:

от наличия артериальной гипертензии // Российский кардиологический журнал, - 2018. 1 (153), - с. 43–50.

[5] Schunkert, H. Genetics of CVD in 2017: expanding the spectrum of CVD genetics // Nat Rev Cardiol, - 2018. 15, - p. 77–8

myocardial infarction, ischemic heart disease, type 2 diabetes mellitus.[6]

Platelet aggregation plays a central role in the pathogenesis of ischemic heart disease, ischemic stroke, peripheral artery disease, and acute thrombosis. ITGB3 gene polymorphism increases platelet aggregation. It is possible to confirm that the significance of gene polymorphisms at different stages of atherogenesis is not the same based on the obtained results. In general, the authors have demonstrated the impact of fibrinogen gene polymorphisms (FGB A>G) on the progression of the atherosclerotic process.[7]

Fibrinogen is the main ligand of the platelet receptor. The combination of the integrin ITGB3 gene polymorphism with the fibrinogen FGB causes thrombus formation and poses the greatest risk for coronary artery disease.[8] The interaction of the integrin ITGB3 with fibrinogen is a vital reaction on which thrombus formation depends.[9]

Concluding the review of the available literature data, it should be noted that the concept of risk factors such as ischemic heart disease and arterial hypertension is an integral part of modern medicine and has led to the development of effective treatment and prevention strategies in clinical practice. Advances in molecular genetics over the past two decades, especially genome-wide association studies, have made it possible to calculate disease risk, predict treatment effectiveness, and improve preventive measures using new tools.

The purpose of the study: Assessment of clinical-genetic aspects in patients with arterial hypertension, ischemic heart disease and type

[6] Netiazhenko, V., Liakhotska, A.V. Hypercholesterolemia as a factor in the risk stratification of patients with hypertension depending on the ITGA2 gene polymorphism // european heart journal, - 2021. 42(1), - p. ehab724.2331

[7]Шумилов, Д.С. Полиморфизмы генов иитегринов ITGA2 и ITGB3, ассоциированных с риском развития коронарного атеросклероза у жителей Республики Адыгея // - Майкоп: Вестник Адыгейского государственного университета, - 2015. 3 (166), - с. 82-87.

[8] Butnariu, L.I. Etiologic Puzzle of Coronary Artery Disease: How Important Is Genetic Component? / L.I. Butnariu, L. Florea, M.C. Badescu [et al.] // Life, - 2022. 12(6), - p. 865

[9] Литвинов Р.И. Динамика белок-белковых взаимодействий на уровне единичных молекул на примере тромбоцитарного интегрина αIIbβ3 и фибриногена) Пенсильвания, США 2013 года

2 diabetes mellitus, depending on the carrier of genetic polymorphisms of integrin genes (ITGA2, ITGB3)

Tasks of the research:

1. Study of distribution of integrin ITGA2, ITGB3 and fibrinogen FGB genes in the main and control groups with arterial hypertension.
2. Determining the relationship of polymorphisms of integrin ITGA2, ITGB3 and fibrinogen FGB genes with some blood parameters (lipid profile and thrombocytic indices) in patients with arterial hypertension.
3. Determination of association of integrin ITGA2, ITGB3 and fibrinogen FGB genes with electrocardiography (ECG) parameters (QT and corrected QTc interval and sign of left ventricular hypertrophy) in patients with arterial hypertension.
4. Determining the relation between left ventricular diastolic function and left ventricular hypertrophy (interventricular septal thickness (IVSt) and left ventricular posterior wall thickness (LVPWt) with integrin ITGA2, ITGB3 and fibrinogen FGB genes in the studied groups according to echocardiography data.

The main provisions to be defended:

– To determine the frequency of single nucleotide polymorphisms of integrin (ITGA2, ITGB3) and fibrinogen (FGB) genes in patients with arterial hypertension.

– To determine the association of single nucleotide polymorphisms of integrin (ITGA2, ITGB3) and fibrinogen (FGB) genes with ischemic heart disease and type 2 diabetes mellitus in patients with arterial hypertension.

– The identification of a high frequency of dyslipidemia and platelet indices in genotype carriers of the ITGA2, ITGB3 integrin genes and the FGB fibrinogen gene in patients with arterial hypertension.

– The study of the correlation between the changes in electrocardiography and transthoracic echocardiography parameters and the carriage of single nucleotide polymorphisms in the candidate genes ITGA2, ITGB3 integrins, and FGB fibrinogen in patients with arterial hypertension.

– The study of the effect of combined polymorphic variants of the ITGA2, ITGB3 integrin genes, and the FGB fibrinogen gene on the prolongation of the QT interval and the development of left ventricular hypertrophy in patients with arterial hypertension.

– The development and clinical implementation of a comprehensive preventive measure strategy, combining traditional and non-traditional (genetic profiling) methods, for the detection of complications in arterial hypertension.

Scientific novelty of research work:

– For the first time in Azerbaijan, the polymorphisms of integrin and fibrinogen candidate genes and their association with arterial hypertension (AH) have been studied in patients with arterial hypertension.

– For the first time in Azerbaijan, the relationship between the carriage of integrin and fibrinogen gene polymorphisms and lipid profile as well as platelet indices has been studied in patients with arterial hypertension.

– For the first time in Azerbaijan, the correlation between the carriage of integrin and fibrinogen gene polymorphisms and changes in electrocardiography and transthoracic echocardiography has been studied and analyzed.

Practical significance of the study:

1. The polymorphisms of integrin and fibrinogen candidate genes and their association with arterial hypertension, cardiovascular disease, and type 2 diabetes have been studied.
2. The genetic markers of the integrin and fibrinogen genes studied are associated with the clinical features of arterial hypertension: in carriers of the mutant heterozygous C/T genotype of the ITGA2 integrin gene, the normal homozygous T/T genotype of the ITGB3 integrin gene, and the normal homozygous G/G genotype of the FGB fibrinogen gene, a high frequency of dyslipidemia has been identified. Therefore, these genotypes can be considered predictors of dyslipidemia.
3. An increase in platelet indices has been observed in carriers of the T allele of the ITGA2 integrin gene.

4. In patients with arterial hypertension and left ventricular hypertrophy, the presence of homozygous variants in the three studied genes (the mutated homozygous T/T genotype of the ITGA2 integrin gene, the normal homozygous T/T genotype of the ITGB3 integrin gene, and the mutated homozygous A/A genotype of the FGB fibrinogen gene) indicates a higher risk, proving its clinical significance. This suggests that more intensive and early prevention should be recommended.
5. The analysis of the associations of polymorphic variants of integrin and fibrinogen genes, along with the identification of molecular-genetic markers in patients with arterial hypertension, ischemic heart disease, and type 2 diabetes, will enable medical genetic counseling in the population.

Approval of the dissertation materials. The main provisions of the dissertation were included in the lecture and seminar program in the post-diploma study course in cardiology of Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev. The dissertation work was discussed at the inner-departmental meeting of Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev on 25.01.2024 and the Scientific seminar on cardiology specialty 3218.01 of the ED 2.27 Dissertation Council operating under Azerbaijan Medical University on 21.06.2024.

Publications. The results of the dissertation have been published in journals reviewed by the Supreme Attestation Commission over the past 5 years. 9 articles (7 local, 2 international journals) and 5 theses (4 local, 1 international) were published on the subject of the dissertation.

The results of the research were reported and discussed:

1. At the 37th European Cardiology Conference (United Kingdom, October 31, 2022).
2. Poster presentation at the XI National Congress of the Azerbaijan Society of Cardiology (Baku, November 9-11, 2022)
3. Presented at the international scientific-practical conference dedicated to the 100th anniversary of national leader Haydar Aliyev at the Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev (Baku, May 5, 2023).

4. Poster presentation at the European Society of Cardiology Heart Failure international conference (Prague-Chechia, May 19-23, 2023).

The volume and structure of the dissertation work.

The dissertation is written on 176 pages and consists of the following parts: introduction - 17.201 characters, chapter I (literature review) - 49.662 characters, chapter II (material and methods)- 14.283 characters, chapter III - 25.619 characters, chapter IV - 82.435 characters, summary – 23.615 characters, results – 2.062 characters, practical recommendations - 1032 characters, list of references and list of abbreviations. The literature list included 179 bibliographic sources, including 9 local and 170 foreign languages. The total volume of the dissertation with signs (without taking into account tables, graphs and the bibliography) - consists of 215.909 signs, 42 tables, 23 figure and 2 pictures.

MATERIALS AND METHODS OF THE STUDY

The work was performed at the Azerbaijan State Advanced Training Institute for Doctors named after A. Aliyev, Special Treatment Health Complex, Shafa Therapeutic Diagnostic Center from 2019-2022.

A total of 100 patients were examined, 76 of them were the main group with arterial hypertension, and 24 patients were without arterial hypertension and comorbidities (IHD and T2DM) (control group).

İnclusion criteria: The study included 100 healthy patients aged 30-70 years, of both sexes,who were diagnosed with arterial hypertension, concomitant ischemic heart disease, type 2 diabetes mellitus and were clinically healthy.

Exclusion criteria: patients younger than 20 years and older than 80 years, pregnancy, patients with congenital heart defects, congenital and acquired hematologic diseases, patients receiving chemotherapy, oncological patients, patients with mental disorders and patients with chronic kidney failure.

The main group with arterial hypertension was divided into 3 clinical subgroups according to the presence of concomitant diseases

(IHD and T2DM): 29 patients with AH in the first subgroup, 23 patients with AH and IHD in the II subgroup, and 24 patients with AH+IHD+T2DM in the III subgroup were included.

The examination of patients included the collection of anamnesis, anthropometric indicators, instrumental, laboratory and genetic examinations.

In order to confirm the diagnosis of arterial hypertension, a history of arterial hypertension, use of antihypertensive drugs or high indicators of systolic and diastolic arterial pressure were accepted as one of the criteria. The arterial pressure of the patients in the study subgroups was predominantly Grade II, with a small portion classified as Grade III.

Comparative study subgroups II and III included patients with a pre-diagnosis of ischemic heart disease or a diagnosed ischemic heart disease during the study period (mainly stable angina pectoris functional class II-III according to the Canadian Cardiovascular Society).

All patients included in the study received optimal medical treatment based on the protocols recommended by the European Society of Cardiology and the Ministry of Health of Azerbaijan. The main treatment of patients with arterial hypertension in the main group was angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Patients with IHD were additionally treated with antiplatelets, antilipidemic drugs and beta-blockers. Patients with T2DM were under the care of an endocrinologist.

Electrocardiography (resting ECG) was performed on a Cardioline ar2100view device with standard 12 leads.

Left ventricular hypertrophy was determined by the ECG method based on the Sokolow-Lyon and Peguero-Lo Presti criteria. Corrected QTc-interval was calculated by Bazett's formula (ms).

Transthoracic Echocardiography and Dopplerography was carried out by the standard method with the "Acuson Juniper" stationary ultrasound machine. The parameters of the systolic and diastolic function of the left ventricular myocardium were determined by TTE and dopplerography methods.

Estimation of left ventricular ejection fraction was performed by Simpson's method.

Diastolic dysfunction and its types in the patients included in the study were determined based on the 2016 recommendations of the American Society of Echocardiography in collaboration with the European Cardiovascular Imaging Association. During the assessment of diastolic function, early and late maximum velocities of transmitral blood flow (E, A), E/A ratio, TRvel >2/8 m/s, as well as tissue doppler examination of medial e' speed and E/e' indicators of the mitral annulus were measured.

For the assessment of left ventricular hypertrophy, the left ventricular myocardial mass (LVMM), left ventricular myocardial mass index (LVMi), and the relative wall thickness (RWT) of the left ventricle were calculated.

The 2019 ESC diabetes, prediabetes and cardiovascular disease recommendations developed in collaboration with the EASD were followed during the examination of patients with T2DM. Patients with a history of at least 5 years of diabetes mellitus type 2 were included.

Blood Glucose and HbA1c were determined in serum using Roche Cobas C 111 (Switzerland).

Lipid spectrum indicators were determined in serum using the Roche Cobas C 111 (Switzerland) to measure total cholesterol (TC), triglycerides (TG), high-density lipoproteins (HDL), low-density lipoproteins (LDL), and very low-density lipoproteins (VLDL).

According to the European Society of Cardiology's 2019 recommendations on dyslipidemia, TC, HDL, and TG are recommended for the assessment and further refinement of total cardiovascular risk, as well as part of routine lipid analysis. The target levels for LDL are recommended as follows: for patients in the moderate-risk group: <100 mg/dL, and for patients in the high-risk group (e.g., İHD and T2DM): <70 mg/dL.

Patients in the II and III subgroups of the study were taking medications from the antilipidemic drug group, specifically statins.

The diagnosis of ischemic heart disease was made on the basis of examinations such as ergometry, computed tomography (Agatstone score), coronary angiography (CAG) and/or CT-angiography, and the result were presented.

Genetic studies integrin ITGA2, ITGB3 and fibrinogen FGB genes were identified by massARRAY (Agena Bioscience GmbH, Germany).

Statistical analysis. The research design was analytical; by method, clinical; in terms of scope, selective; by type, scientific; based on the material, prospective; in terms of duration, cross-sectional; and by location, clinically determined. Quantitative and qualitative indicators obtained during the study are variation (t-Student-Bonferroni, U-Mann-Whitney, H-Kruskal-Wallace), discriminant (Chi-square Pearson, odds ratio), dispersion (F-Fisher) and correlation (Rho- Spearman) was carried out in the IBM Statistics SPSS-26 program with the application of methods.

OBTAINED RESULTS AND THEIR DISCUSSION

Distribution of genotypes of integrin ITGA2, ITGB3 and fibrinogen FGB genes.

Consequences of substitution of cytosine nucleotide (C) with thymine (T) polymorphism of the integrin ITGA2 gene: in 76 patients with AH, the normal homozygous C/C genotype was present in 50 patients (69.0%), the altered heterozygous C/T genotype in 17 patients (22.4%), and the altered homozygous T/T genotype was determined in 9 patients (11.8%). Their prevalence in the control group was 12 (50.0%), 6 (25.0%) and 6 (25.0%) patients, respectively (figure1).

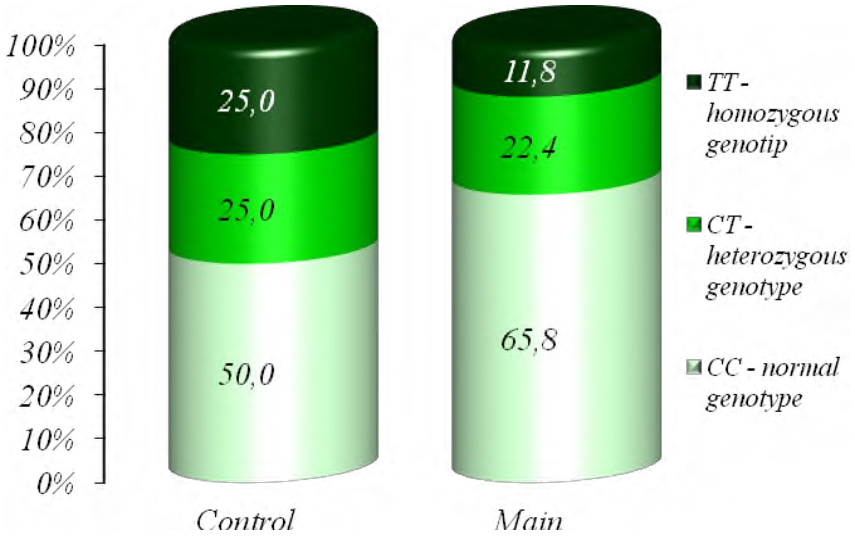

Figure 1. Genotype frequency (%) of ITGA2 gene polymorphism in patients with AH (n=76) and control group (n=24)

Statistical analysis of the odds ratio (OR) of the prevalence of the normal homozygous C/C genotype of the integrin ITGA2 gene showed that the odds ratio of this genotype was 1.9 times greater in the group of patients with arterial hypertension compared to the control group (OR=1.923, 95% CI 0.759-4.874), however, the difference was not statistically significant ($p>0.05$). Compared to the control group, the odds ratio of the altered heterozygous C/T genotype among patients with arterial hypertension was (OR=0.864 95%CI 0.297-2.520, $p>0.05$), that is, the odds ratio of the heterozygous form among patients with arterial hypertension was insignificant. Compared to the control group, the odds ratio of the altered homozygous T/T genotype of the integrin ITGA2 gene was lower (OR=0.403, 95%CI 0.127-1.281, $p>0.05$).

Analysis of the integrin ITGA2 gene polymorphism confirmed the predominance of the normal homozygous C/C genotype in all study subgroups. In subgroup with AH, normal homozygous C/C genotype was determined in 20 patients (69.0%), in subgroup with AH and IHD- in 15 patients (65.2%), and in subgroup with AH, IHD and T2DM - in

15 patients (62.5%). The prevalence of the altered heterozygous C/T genotype was as follows: in subgroup with AH - 5 patients (17.2%), in subgroup with AH and IHD - 5 patients (21.7%), in subgroup with AH, IHD and T2DM - 7 patients (29.2%). The prevalence of the altered homozygous T/T genotype was as follows: in subgroup with AH- 4 patients (13.8%), in subgroup with AH and IHD - 3 patients (13.0%), in subgroup with AH, IHD and T2DM - 2 patients (8.3%) (figure 2).

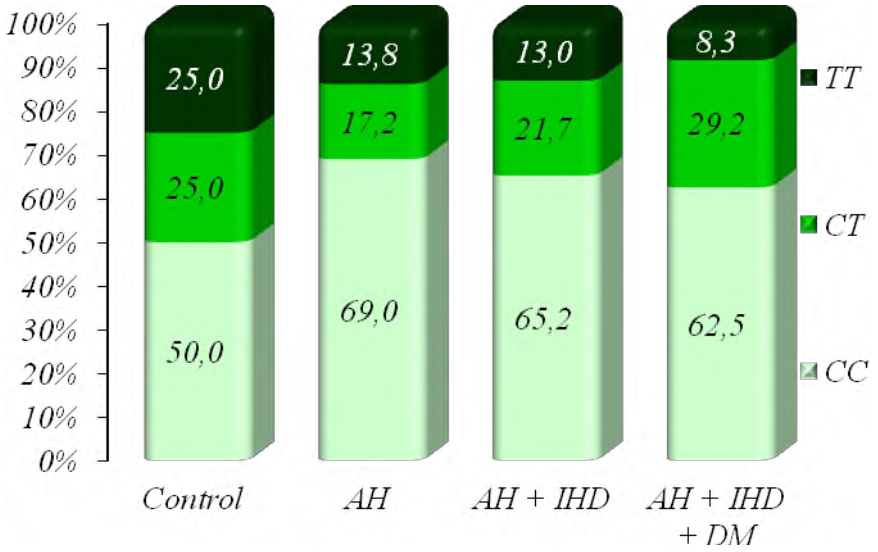

Figure 2. Prevalence(%) of integrin ITGA2 gene genotypes in patients within the study subgroups

Consequences of substitution of thymine nucleotide (T) of integrin ITGB3 gene polymorphism by cytosine (C): according to the genotyping data, in 76 patients with arterial hypertension, the normal homozygous T/T genotype was present in 56 (73.7%), the altered heterozygous T/C genotype – in 16 (21.0%), and the altered homozygous C/C genotype was determined in 4 (5.3%). In the control group, the prevalence of the normal homozygous T/T genotype and the altered heterozygous T/C genotype was 19 (79.2%) and 5 (20.8%) patients, respectively (figure 3).

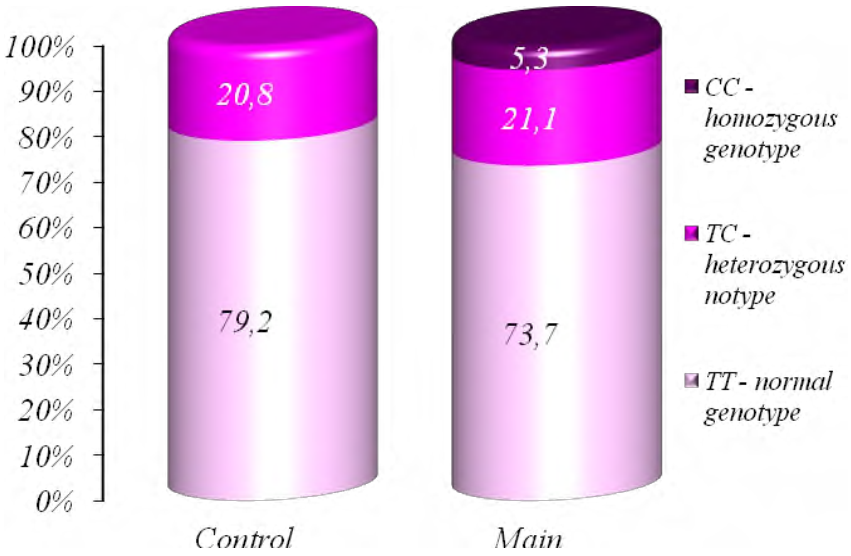

Figure 3. Prevalence (%) of ITGB3 gene polymorphism in patients with AH and in control group

Statistical analysis of the odds ratio (OR) of the prevalence of the normal homozygous T/T genotype of the integrin ITGB3 gene showed that the odds ratio of this genotype was 0,7 times lower in the group of patients with AH compared to the control group (OR=0.737, 95%CI 0.243-2.235), however, the difference was not statistically significant ($p>0.05$). The odds ratio of heterozygous T/C genotype among patients with AH was determined comparing to the control group (OR=1.013 95%CI 0.328-3.134, $p>0.05$), that is, there was no difference in the odds ratio of heterozygous carrier among patients with arterial hypertension.

Analysis of the integrin ITGB3 gene polymorphism confirmed the predominance of the normal homozygous T/T genotype in all study subgroups (figure 4).

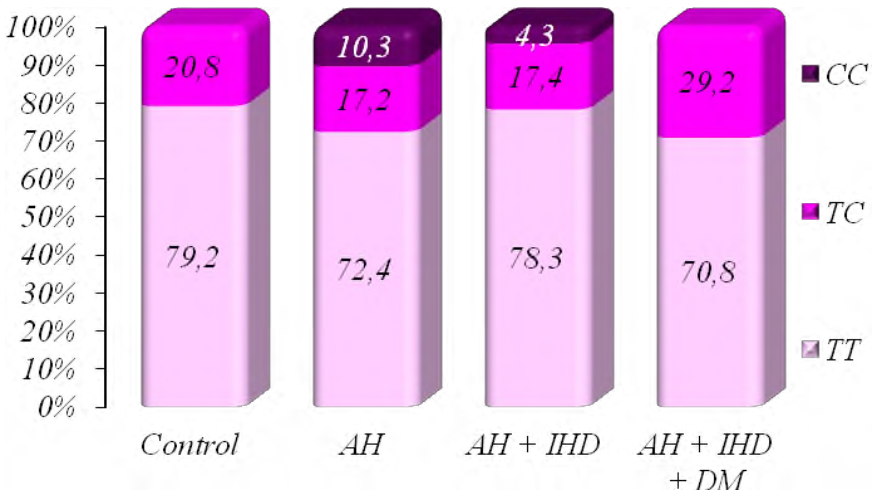

Figure 4. Prevalence of ITGB3 gene genotypes in patients in study subgroups (%)

According to the data from Graph 4, 21 patients with arterial hypertension (72.4%), 18 patients with AH+IHD (78.3%), and 17 patients with AH+IHD+T2DM (70.8%) were carriers of the normal homozygous T/T genotype. In Groups I, II, and III, there were 5 (17.2%), 4 (17.4%), and 7 (29.2%) patients, respectively, who were carriers of the altered heterozygous C/T genotype. In Groups I and II, there were 3 (10.3%) and 1 (4.3%) patients, respectively, who were carriers of the mutant homozygous C/C genotype. No carriers of the mutant homozygous C/C genotype were found in Group III.

Compared to subgroup II, the odds ratio of normal homozygous T/T genotype of integrin ITGB3 gene in subgroup I was slightly lower (OR=0.990, 95%CI 0.233-2.202, p>0.05), and compared to subgroup III, the odds ratio was 1.1 times high (OR=1.081, 95%CI 0.326-3.586, p>0.05). Compared to subgroup II, the odds ratio of altered heterozygous T/C genotype was lower in subgroup I (OR=0.990, 95%CI 0.233-4.202, p>0.05), the same results were obtained compared to subgroup III (OR=0.506, 95%CI 0.137-1.866, p>0.05). Compared to patients of subgroup III, the odds ratio of altered heterozygous T/C

genotype was 1,5 times higher among patients of subgroup II (OR=1.482, 95%CI 0.394-5.579, p>0.05). Compared to subgroup II, the odds ratio of altered homozygous C/C genotype was 2.5 times higher among the patients of subgroup I (OR=2.538, 95%CI 0.246-26.178, p>0.05).

Consequences of substitution of guanine (G) nucleotide of polymorphism of fibrinogen FGB gene by adenine (A): in 76 patients with AH, normal homozygous G/G genotype was determined in 54 patients (71.1%), altered heterozygous G/A genotype in 16 patients (21.0%), altered homozygous A/A genotype in 6 patients (7.9%). The prevalence of normal homozygous G/G and altered heterozygous G/A genotypes in the control group was 14 (58.3%) and 10 (41.7%) patients, respectively (figure 5).

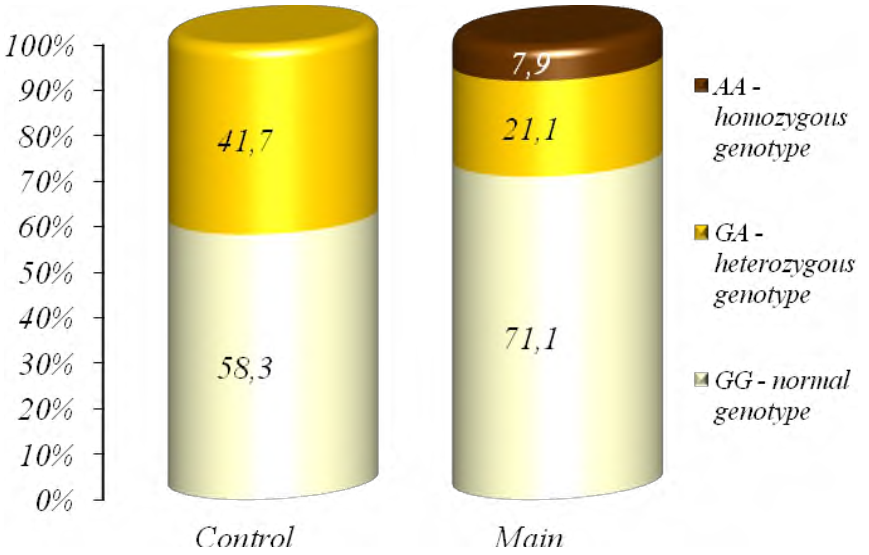

Figure 5. Prevalence of FGB gene polymorphism in patients of the main and control groups in %

Fibrinogen FGB gene polymorphism analysis confirmed the predominance of normal homozygous G/G genotype in all study

groups. In subgroup with arterial hypertension 20 (69.0%) patients was carriers of normal homozygous G/G genotype, 7 (24.1%) patients were carriers of altered heterozygous G/A genotype, and 2 (6.9%) patients were carriers of altered homozygous A/A genotype. In subgroups AH+IHD and AH+IHD+T2DM, 20 (87.0%) and 14 (58.3%) patients, respectively, were carriers of the normal homozygous G/G genotype, 1 (4.3%) and 8 (33.3%) patients were heterozygous G/A genotype carrier, 2 (8.7%) and 2 (8.3%) patients were altered homozygous A/A genotype carriers. In the control group, carriers of the normal homozygous G/G genotype and the altered heterozygous G/A genotype were identified in 14 (58.3%) and 10 (41.7%) patients, respectively. No carriers of the altered homozygous A/A genotype were identified in this group (figure 6).

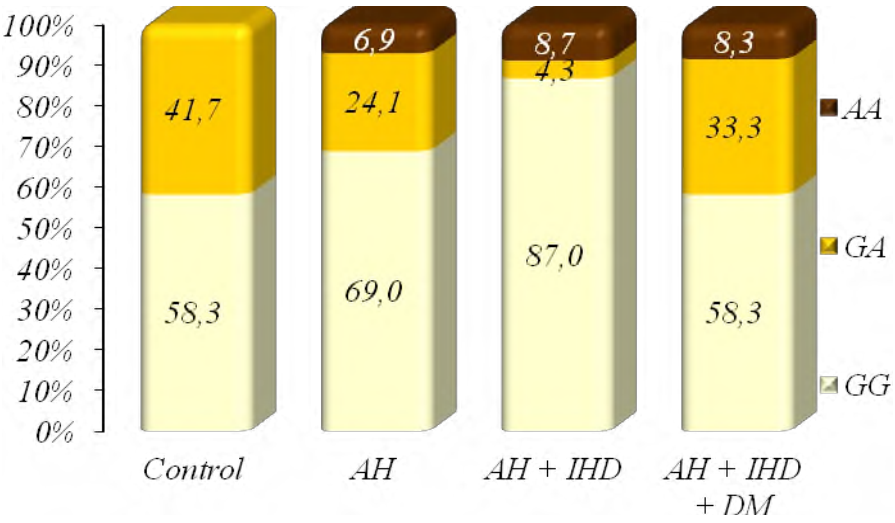

Figure 6. Prevalence of fibrinogen FGB gene genotypes in examined patients (%)

The statistical analysis of the odds ratio (OR) between groups I and II showed that in group I, among patients with the normal homozygous G/G genotype of the fibrinogen FGB gene, the odds ratio was slightly lower (OR=0.333, 95% CI 0.078-1.416, p>0.05).

Compared to group III, the odds ratio for the G/G genotype among patients in group I was 1.6 times higher (OR=1.587, 95% CI 0.513-4.915, p>0.05). In group II, compared to group III, the odds ratio for homozygous G/G genotype carriers was statistically significantly 4.8 times higher (OR=4.762, 95% CI 1.106-20.502, p<0.01). Compared to group II, the odds ratio for the altered heterozygous G/A genotype of the fibrinogen FGB gene in patients from group I was 7.0 times higher (OR=7.00, 95% CI 0.794-61.743, p<0.05), whereas it was slightly lower when compared to group III (OR=0.636, 95% CI 0.191-2.116, p>0.05). The odds ratio for altered heterozygous G/A genotype carriers among patients in group II was lower compared to group III (OR=0.091, 95% CI 0.010-0.801, p<0.05). Compared to group II (with hypertension and cardiovascular diseases), the odds ratio for patients with the altered homozygous A/A genotype in group I (with hypertension) was almost equal (OR=0.778, 95% CI 0.101-5.989, p>0.05). The statistical analysis of the odds ratio (OR) between groups I and III indicated that the odds ratio for patients with the altered homozygous A/A genotype was slightly lower (OR=0.815, 95% CI 0.106-6.262, p>0.05). Compared to group III, the odds ratio for patients with the altered homozygous A/A genotype in group II was 1.0 times higher (OR=1.048, 95% CI 0.135-8.131, p>0.05). Relationship of integrin ITGA2, ITGB3 and fibrinogen FGB gene polymorphisms with the studied indicators.

The Relationship of Integrin ITGA2, ITGB3, and fibrinogen FGB gene polymorphisms with the studied indicators.

It is known that lipid metabolism disorders play an important role in the development of cardiovascular diseases.

We studied the relationship between lipid metabolism parameters and polymorphism of integrin ITGA2, ITGB3 and fibrinogen FGB genes.

According to the obtained results, the level of total cholesterol (TC) was relatively high in heterozygous C/T genotype carriers of the integrin ITGA2 gene (Me=202; IQ(165-232)). The highest levels of TG and VLDL were found in altered homozygous T/T genotype carriers of the integrin ITGA2 gene, (Me=161; IQ(89-175) and

Me=32.2; IQ(18.0-35.0) respectively). High levels of LDL were found in carriers of the altered heterozygous C/T genotype (Me=97; IQ(72.0-129)). In the main group, low values of HDL were observed in patients with homozygous T/T genotype carriers (Me=34; IQ(32-50)). The high level of atherogenic index (AI) was identified in patients with altered heterozygous C/T genotype (Me=3.7; IQ(2.5-5.4)).

The T allele of the integrin ITGA2 gene can be considered a predictor of lipid metabolism disorders in hypertensive azerbaijani patients.

Results of lipid profile parameters in arterial hypertension patients with different ITGB3 gene polymorphisms.

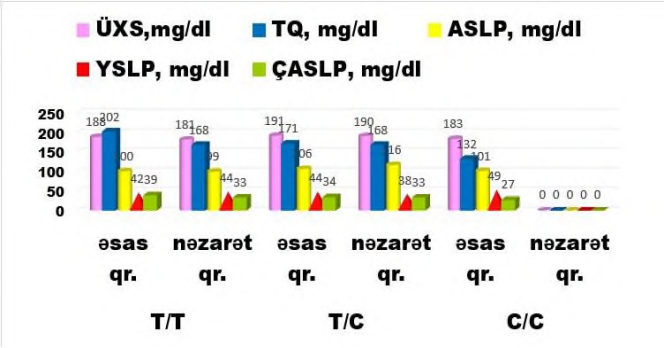

Figure 7. Lipid profile parameters in baseline and control group patients with different ITGB3 polymorphisms

As can be seen from figure 7, there was no significant difference in the level of total cholesterol in carriers of integrin ITGB3 gene genotypes in the main group. In the main group, the highest levels of TG and VLDL were determined in normal homozygous T/T genotype carriers, (Me=151; IQ(105-266) and Me=30.4; IQ(21.3-53.1) respectively).

A relatively high level of LDL was found in carriers of the altered homozygous C/C genotype (Me=103 IQ(81.0-120.5)). A high level of AI was found in patients with the altered heterozygous T/C genotype in the main group (Me=3.8; IQ(2.2-4.3)).

The T allele of the integrin ITGB3 gene can be the leading link in the development of arterial hypertension and its complications in azerbaijani patients.

Association between fibrinogen FGB gene polymorphisms and lipid profile parameters in patients with arterial hypertension.

High levels of TC, TG and VLDL were identified in the altered heterozygous G/A genotype carriers of the fibrinogen FGB gene, (Me=202; IQ(147-237), Me=151; IQ(131-190) and Me=30.4; IQ(25.2-37.7) respectively). In the main group, patients with altered homozygous A/A genotype had a high level of LDL (Me=98.5; IQ (60.0-158.0)). Normal homozygous G/G genotype was associated with low level of HDL in the main group (Me=39; IQ(33-49)). A high atherogenic index level was recorded in patients with normal homozygous G/G genotype (Me=3.8; IQ(2.2-4.6)).

Therefore, the G allele of the fibrinogen FGB gene is the leading link in the formation of dyslipidemia in Azerbaijani patients with arterial hypertension.

Integrin alpha 2 gene (ITGA2) is involved in platelet activation. Platelets are involved in the initiation of endogenous hemostasis and effective regeneration of the endothelium after vascular injury. Platelet functions, such as adhesion, activation, aggregation, and interaction with coagulation factors, control and influence vascular injury sites.

The results obtained confirm that the platelet (PLT) levels in the patients of the main group were within the normal range. However, the average PLT level was relatively higher in carriers of the normal homozygous C/C genotype of the ITGA2 gene (Me=201; IQ (175.0-234.0)), in carriers of the heterozygous T/C genotype of the ITGB3 gene (Me=219.0; IQ (184.0-241.5)), and in carriers of the mutant homozygous A/A genotype of the FGB gene (Me=210.0; IQ (164.0-287.0)).

The average level of mean platelet volume (MPV) was higher in carriers of the mutant homozygous T/T genotype of the ITGA2 gene (Me=8.70; IQ (8.00-9.40)), in carriers of the mutant homozygous C/C genotype of the ITGB3 gene (Me=8.55; IQ (7.60-9.20)), and in

carriers of the normal homozygous G/G genotype of the FGB gene (Me=8.50; IQ (7.90-9.20)).

In all cases, the MPV value was within the average reference interval (8.0-13.0 fl).

The level of platelet distribution width (PDW) was within the normal range in the patients of the main group. However, the average PDW level was relatively higher in carriers of the mutant homozygous T/T genotype of the ITGA2 gene (Me=11.00; IQ (10.00-12.10)), in carriers of the mutant homozygous C/C genotype of the ITGB3 gene (Me=11.35; IQ (10.30-16.80)), and in carriers of the mutant heterozygous G/A genotype of the FGB gene (Me=10.60; IQ (10.05-13.85)).

The average level of plateletcrit (PCT) showed minimal differences among the carriers of various polymorphisms of the ITGA2 gene. Additionally, the average PCT level was relatively higher in carriers of the mutant heterozygous T/C genotype of the ITGB3 gene (Me=0.18; IQ (0.15-0.20)) and in carriers of the mutant homozygous A/A genotype of the FGB gene (Me=0.18; IQ (0.13-0.21)).

The average level of the ratio of large platelets to total platelet count (LPCR) was relatively higher in carriers of the mutant homozygous T/T genotype of the ITGA2 gene (Me=20.60; IQ (14.90-24.90)), in carriers of the mutant homozygous C/C genotype of the ITGB3 gene (Me=21.34; IQ (16.45-28.61)), and in carriers of the mutant homozygous A/A genotype of the FGB gene (Me=18.20; IQ (14.80-24.20)).

Statistical integrity was noted among ITGA2 gene polymorphism, MPV, and LPCR index in subgroup of patients with arterial hypertension (P=0.036 and p=0.021).

In the arterial hypertension and ischemic heart disease subgroup, compared to normal homozygous T/T genotype carriers of the ITGB3 gene, a statistically significant increased association of PCT with the altered heterozygous T/C genotype was found (p=0.035).

A positive correlation coefficient was determined between the T allele of the ITGA2 gene with the MPV, PDWsd and LPCR indicators in the arterial hypertension subgroup, (Rho=0.467

P=0.011, Rho=0.427 p= 0.021, Rho=0.525 p=0.004 respectively) (figure 8).

Statistical integrity of fibrinogen FGB gene polymorphism between platelet indices was not found.

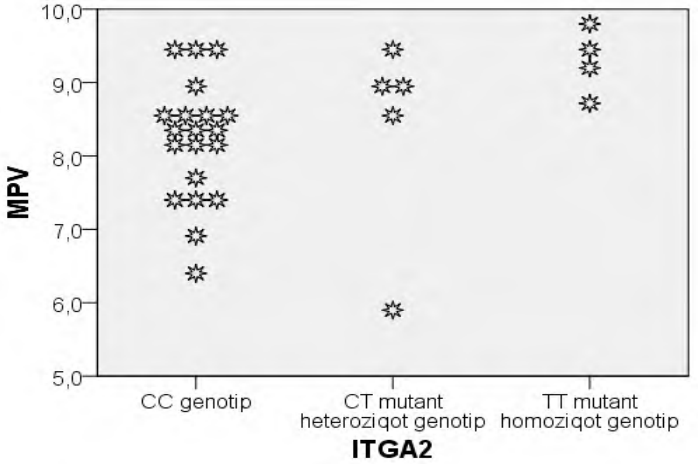

Figure 8. Correlation between platelet index (MPV) and integrin ITGA2 gene polymorphism

It is known that the QT interval, an electrophysiological parameter of heart activity, reflects the structural and functional state of the myocardium, electrical systole, which is reflected in the ECG as a change in the QT interval and QTc parameter. Normal values for the QTc interval are considered to be 320-440 ms.

The study showed that the QT interval in the hypertensive patients we examined did not exceed these values for different polymorphic variants of integrin ITGA2, ITGB3 and fibrinogen FGB genes. However, according to our data, the longest QT interval was observed in carriers of the normal homozygous genotype C/C carriers of the integrin ITGA2 gene, altered heterozygous genotype T/C carriers of the integrin ITGB3 gene, and altered homozygous A/A genotype carriers of the fibrinogen FGB gene (figure 9).

According to our data, the QT interval significantly exceeded the control value in hypertensive patients with IHD and T2DM.

Longer QTc interval in patients of subgroup with AH was identified in altered homozygous T/T genotype carriers of ITGA2 gene (Me=414; IQ(386-425)), altered heterozygous C/T genotype carriers among subgroup with arterial hypertension and ischemic heart disease patients (Me=396; IQ(380-404)) and normal homozygous C/C genotype carriers among subgroup with arterial hypertension, ischemic heart disease and diabetes mellitus type 2 patients (Me=425; IQ(396-447)).

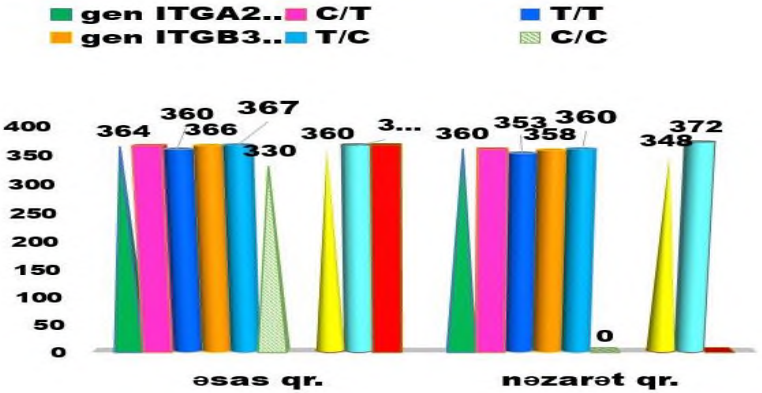

Figure 9. QT interval in integrin ITGA2, ITGB3 and fibrinogen FGB gene polymorphisms carriers

In patients of subgroup AH and AH+IHD, the relatively long QTc interval was determined in altered heterozygous T/C genotype of the integrin ITGB3 gene carriers (Me=413; IQ(407-425), Me=397; IQ(356-413) respectively); and among patients of subgroup AH+IHD+T2DM, in the carriers of normal homozygous T/T genotype (Me=425; IQ(396-436)).

In patients of subgroups AH and AH+IHD, the relatively long QTc interval was determined in carriers of altered homozygous A/A genotype of altered fibrinogen FGB gene, (Me=425; IQ(425-425) and Me=423; IQ(410-436) respectively); and among patients of the subgroup AH+IHD+T2DM in altered heterozygous G/A genotype carriers (Me=426; IQ(415-442)).

The carriers of altered homozygous C/C genotype of integrin ITGB3 had a significantly lower QT interval compared to normal

homozygous T/T genotype carriers (p=0.013) and altered heterozygous T/C genotype carriers.

During the comparison of subgroups, a statistically significant correlation was observed between the presence or absence of altered genotypes (heterozygous, homozygous) of the fibrinogen FGB gene and elevated levels of the QTc interval (pH=0.020).

In the arterial hypertension+ischemic heart disease subgroup, a positive correlation coefficient was found between the QTc interval and the A allele of the fibrinogen FGB gene (Rho=0.428, P=0.041) (figure 10).

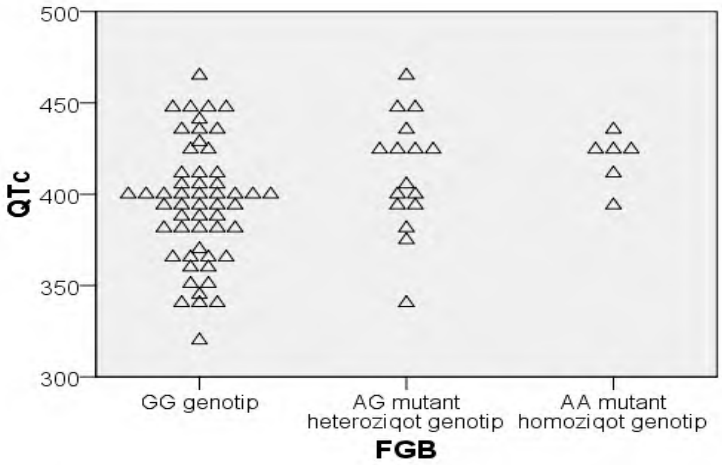

Figure 10. Correlation between genotypes of fibrinogen FGB gene polymorphism and QTc interval

Arterial hypertension is the most pathological cause of increased loading, which leads to thickening of the left ventricular walls and left ventricular hypertrophy (LVH).

In total, 60 of the 100 examined patients, showed symptoms of left ventricular hypertrophy.

We analyzed the association of integrin ITGA2, ITGB3 and fibrinogen FGB gene polymorphisms with left ventricular hypertrophy. Among the patients of the main group, normal homozygous C/C genotype and altered homozygous T/T genotype carriers of ITGA2,

(p=0.019) (p=0.004) respectively, as well as normal homozygous T/T genotype carriers of ITGB3 gene and carriers of the normal homozygous G/G genotype of the FGB gene had a significant difference in the number of patients with left ventricular hypertrophy (p<0.001).

Left ventricular hypertrophy was observed in the subgroup of patients with AH and AH+IHD+T2DM in carriers of the altered homozygous T/T genotype of the integrin ITGA2 gene.

According to the data presented in Figure 11, a significant difference was observed in the number of patients with left ventricle hypertrophy among carriers of the altered homozygous A/A genotype of the fibrinogen FGB gene in the subgroup of patients with arterial hypertension (p=0.048) (figure 11).

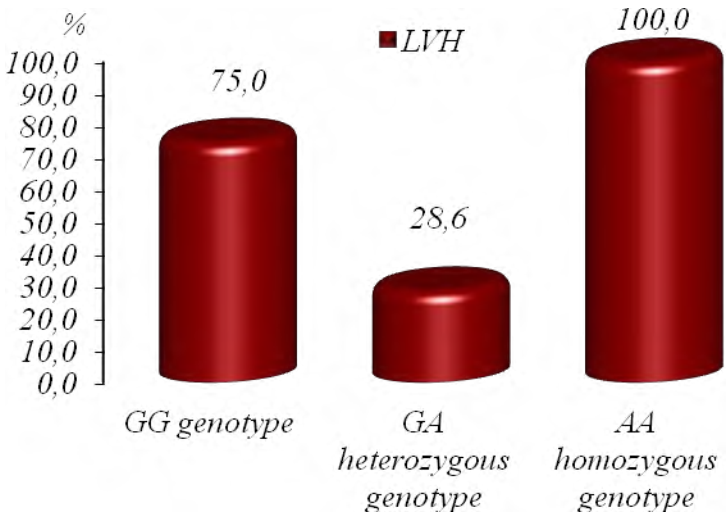

Figure 11. Incidence of left ventricular hypertrophy (LVH) in patients of the AH subgroup based of the genotypic carriers of fibrinogen FGB gene

We investigated the levels of interventricular septal thickness (IVS) and left ventricular posterior wall thickness (LVPW) in carriers of different genotypes of the ITGA2, ITGB3, and FGB genes in a subgroup of patients. İn carriers of the ITGA2 and ITGB3 genes,

the average values of these indicators did not differ significantly from each other. In the subgroup of AH + IHD + T2DM patients, the average value of IVS was significantly higher in carriers of the normal homozygous G/G genotype of the FGB gene compared to carriers of the altered homozygous A/G genotype (pH = 0.034).

As shown in figure 12, in the main group of patients, the mean value of interventricular septal thickness (IVSt) was found to be statistically significantly higher in carriers of the altered homozygous A/A genotype of the FGB gene (P_H=0.029). In carriers of the altered heterozygous G/A genotype of the fibrinogen FGB gene, the mean IVSt value was significantly higher than that in normal homozygous G/G carriers (p=0.045).

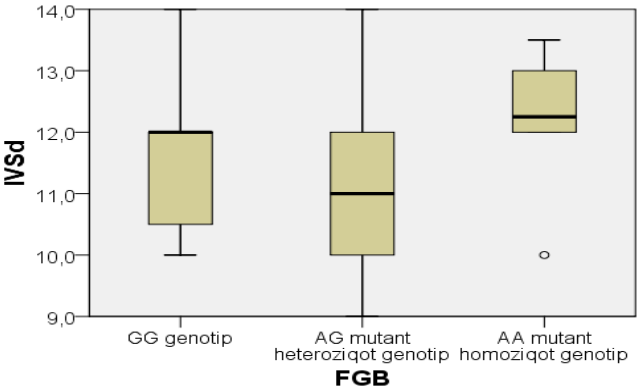

Figure 12. The association between genotypes carriers of the fibrinogen FGB gene and IVSt in the main group of patiets

Among the patients in the subgroup with arterial hypertension, the relatively high value of IVSt was more common in carriers of the altered heterozygous C/T genotype of the ITGA2 gene (Me=12.0; IQ (11.5-13.0)); it was found in carriers of the normal homozygous T/T genotype of the ITGB3 gene (Me=12.0; IQ (11.0-13.0)) and in carriers of the altered homozygous A/A genotype of the FGB gene (Me=12.5; IQ (12.0-13.0)).

In subgroup with AH+IHD, LV PWTt and IVSt were at the same level among genotypes of the ITGA2 gene, a relatively high level of

interventricular septal thickness was found in carriers of the normal homozygous T/T genotype of the integrin ITGB3 gene (Me=12.0; IQ(12.0-12.0)).

In the subgroup with AH+IHD+T2DM, relatively high values of IVSt were found in carriers of the altered homozygous T/T genotype of the ITGA2 gene (Me=13.0; IQ (12.0-14.0)); in carriers of the altered heterozygous T/C genotype of the ITGB3 gene (Me=12.0; IQ(10.0-14.0)); and in carriers of the normal homozygous G/G genotype of the FGB (Me=12.0; IQ (12.0-13.0)). Relatively high value of LV PWT were found in carriers of the altered homozygous T/T genotype of the gene ITGA2 (Me=13.0; IQ(12.0-14.0)); and in carriers of the normal homozygous G/G genotype of the FGB (Me=11.0; IQ(10.0-11.0)). No differences were found among integrin ITGB3 gene genotype carriers.

In the examined patients, predominantly Grade I diastolic dysfunction (impaired relaxation) was detected. We investigated the levels of E, A, E/A, e', and E/e' in carriers of different genotypes of the ITGA2, ITGB3, and FGB genes in the studied subgroup of patients.

Low values of the ratio (E/A) between early and late diastolic mitral flow velocities were found in carriers of the altered heterozygous C/T genotype of the integrin ITGA2 gene (Me=0.70; IQ(0.70-1.40)); in subgroups with AH and AH+IHD, carriers of the homozygous C/C genotype of the integrin ITGB3 gene were identified, (Me=0.70; IQ(0.60-1.50) and Me=0.70; IQ(0.70-0.70) respectively). Low values of the E/A ratio were found in carriers of the normal homozygous G/G genotype of the fibrinogen FGB gene in subgroups with AH+IHD+T2DM (Me=0.70; IQ(0.70-1.50)).

The high value of the E/e' indicator was found in subgroup AH+IHD+T2DM among carriers of the altered homozygous T/T genotype of the integrin ITGA2 gene (Me=15.3; IQ(12.5-18.0)); in subgroup with AH+IHD, carriers of the homozygous T/T genotype of the ITGB3 gene were identified (Me=12.0; IQ(8.0-13.0)). A relatively high value of the E/e' indicator was found in subgroup with AH+IHD among carriers of the altered homozygous A/A genotype of the fibrinogen FGB gene (Me=15.5; IQ(15.0-16.0)).

In the arterial hypertension subgroup, a positive correlation coefficient found between diastolic dysfunction (E/e' ratio) and altered genotypes (heterozygous, homozygous) of the ITGB3 gene, with value of (Rho=0.399 P=0.035) (figure 13).

According to the data in figure 14, a statistically significant difference was found in the presence of diastolic dysfunction (DD) only in subgroup with arterial hypertension, particularly in patients with integrin ITGB3 gene altered heterozygous T/C genotype and homozygous C/C genotype ($P\chi^2$=0.039, P_H=0.043).

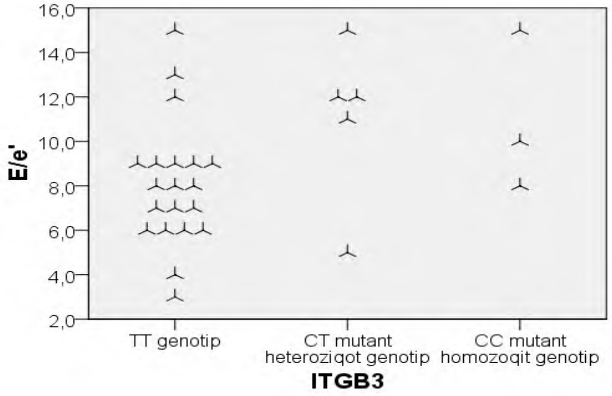

Figure 13. Correlation between the C allele of the integrin ITGB3 gene and the parameter of diastolic function (E/e' ratio)

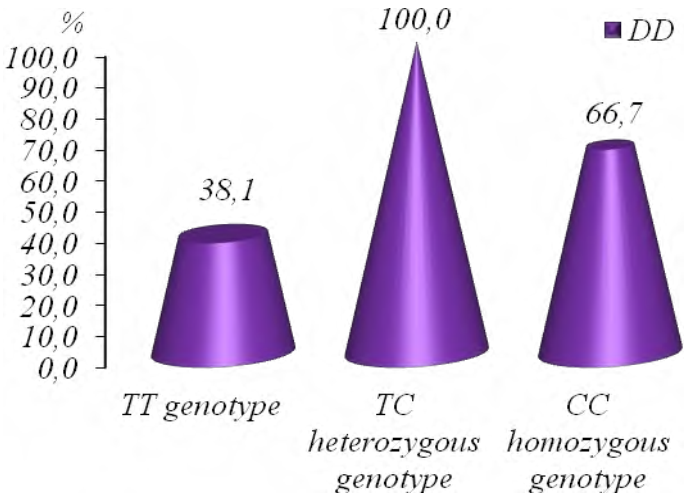

Chart 14. Prevalece of diastolic dysfunction in subgroup AH among carriers of the altered heterozygous genotype of ITGB3 gene (%)

The obtained results allow us to conclude that the identification of polymorphisms of ITGB3 and FGB genes in patients with arterial hypertension (especially when associated with IHD and T2DM) may be related to the thickness of the İVS and the risk of developing diastolic dysfunction.

Based on the results of our research, identifying early predictors of hypertension and its cardiovascular complications enables timely prediction of complications and the implementation of preventive measures. Current genetic-molecular studies complement rather than replace the value of clinical, laboratory and instrumental examinations. In fact, these assessments assist in identifying early predictors of diseases and forecasting potential complications.

RESULTS

1. The prevalence of integrin ITGA2 gene in the main group of patients with arterial hypertension was as follows: normal homozygous C/C genotype 65.8%, altered heterozygous C/T

genotype 22.4%, altered homozygous T/T genotype 11.8%; the distribution frequency of the ITGB3 gene was: normal homozygous T/T genotype 73.7%; altered heterozygous T/C genotype 21.0%, altered homozygous C/C genotype 5.3%. The distribution frequency of FGB gene was: normal homozygous G/G genotype 71.1%, altered heterozygous G/A genotype 21.0%, altered homozygous A/A genotype 7.9%. [1, 2, 3, 4, 5, 6, 8, 10, 11, 12, 16]

2. In the main group of patients, the incidence of dyslipidemia was higher among carriers of the altered heterozygous C/T genotype of the ITGA2 gene, the altered heterozygous T/C genotype of the ITGB3 gene, and the altered heterozygous G/A genotype FGB gene. In this group of patients, a statistically significant relationship was observed between the genotypes of the ITGA2 gene and the MPV and LPCR indicators, with value of, (P=0.036) (Rho=0.467; p=0.011 and P=0.021 Rho=0.525; p=0.004) respectively. A statistically significant increased in PCT was associated with the altered heterozygous T/C genotype (p=0.035) in patients with arterial hypertension and ischemic heart disease compared to carriers of the normal homozygous T/T genotype of the ITGB3 gene.[8, 14, 15, 16, 17]
3. A longer QTc interval was recorded in the main group of patients who were carriers of the altered homozygous A/A genotype of the FGB fibrinogen gene, and this finding was statistically significant (p=0.020). A positive correlation coefficient was found between the A allele carrier of the FGB gene and the QTc interval (Rho=0.271; P=0.018). In the arterial hypertension and arterial hypertension, ischemic heart disease and type 2 diabetes mellitus subgroup, a higher prevalence of left ventricular hypertrophy was observed in carriers of the altered homozygous T/T genotype of the ITGA2 gelowne. Additionally, in the arterial hypertension subgroup, left ventricular hypertrophy was noted in carriers of the altered homozygous A/A genotype of the FGB gene, and this finding was statistically significant (p=0.048). [7, 13, 16]

4. In carriers of the altered heterozygous G/A genotype of the FGB gene, the average IVSd value was significantly higher than in carriers of the normal homozygous genotype G/G (p=0.045). In the main group of patients, left ventricular diastolic dysfunction was statistically significantly associated with the carriage of the altered heterozygous T/C genotype of the ITGB3 gene (p=0.016). [7, 16, 17]

PRACTICAL RECOMMENDATIONS

1. For patients with arterial hypertension, in addition to traditional diagnostic methods (BP measurement, laboratory-clinical, and instrumental indicators), it is recommended to study the polymorphism of integrin and fibrinogen candidate genes as predictors of cardiovascular complications.
2. Studying the polymorphisms of integrin and fibrinogen genes as predictors of thrombus formation will help identify risk groups for the development of cardiovascular pathology among patients in a timely manner.
3. Implementing a range of preventive measures in a group of patients with arterial hypertension who have a high individual genetic risk for thrombus formation and the development of dyslipidemia.
4. Studying the polymorphisms of the ITGA2, ITGB3 integrin genes, and the FGB fibrinogen gene is essential for the early detection of complications in patients with arterial hypertension.
5. The analysis of the associations of polymorphic variants of integrin and fibrinogen genes, along with the identification of molecular-genetic markers in patients with arterial hypertension, ischemic heart disease, and type 2 diabetes, is necessary for medical genetic counseling within the population.

LIST OF PUBLISHED SCIENTIFIC WORKS ON THE TOPIC OF THE DISSERTATION

1. Arterial hipertoniyalı xəstələrdə inteqrin gen polimorfizmi və ürəyin işemik xəstəliyinin riski // - Bakı: AzDHTİ Əziz Məmmədkərim oğlu Əliyevin doğum gününə həsr olunmuş elmi-praktik konfransın məcmuəsı, 2021, - s. 160-161. (həmmüəl. Quliyev F.Ə.).
2. Arterial hipertenziya xəstələrində inteqrinlərin rolu haqqında bəzi anlayışlar // - Bakı: Sağlamlıq jurnalı, 2021, N3 (27), - s.174-177. (həmmüəl. Quliyev F.Ə.).
3. Hipertenziyalı Xəstələrdə Fibrinogen və İnteqrin Genlərinin Polimorf Markerlərinin Genotipik "Ansamblları // - Bakı: Azərbaycan Kardiologiya Jurnalı, 2021, N2, - s.63. (həmmüəl. Quliyev F.Ə.).
4. Aterotrombozun formalaşmasında İnteqrin Fibrinogen Kompleksinin Rolu // - Bakı: Allerqologiya və Klinik İmmunologiya Jurnalı, 2022, N1 (10),- s. 44-47. (həmmüəl. Quliyev F.Ə.).
5. Arterial Hipertenziya, Ürəyin İşemik Xəstəliyi və Şəkərli Diabeti olan xəstələrdə FGB Fibrinogen geninin polimorfizmi // - Bakı: Azərbaycan Kardiologiya Jurnalı, 2022, N1 (21), - s.29-33.
6. The role of polymorphism of the fibrinogen gene FGB G (-455) A in the development of myocardial ischemia in patients with type 2 diabetes mellitus in Azerbaijan // - United Kingdom: 37 European Cardiology Conference, 2022.
7. Hipertenziyalı xəstələrdə ITGA2 inteqrin geninin **(**C759 C>T) müxtəlif genotiplərinin daşıyıcılarında sol mədəcik hipertrofiyası əlamətlərinin rast gəlmə tezliyi // - Bakı: Azərbaycan Kardiologiya Cəmiyyətinin XI Milli Konqresi, 2022.
8. Идентификация однонуклеотидных полиморфизмов гена интегрина ITGA2 и их ассоциация с тромбоцитами у пациентов с артериальной гипертензией // - Россия: Международный журнал сердца и сосудистых заболеваний, 2022, N-36 (10), с. 13-20. (həmmüəl. Quliyev F.Ə., Qafarov İ.A.).

9. Arterial hipertenziya və piylənməsi olan xəstələrdə integrin gen ITGB3 polimorfizminin təhlili // - Bakı: Akademik Zərifə Xanım Əliyevanın 100 İllik Yubileyinə Həsr Olunmuş Elmi-Praktik Konfransın Məcmuası, 2023, - s.111-113.

10. Fibrinogen Gen Polimorfizmi Hipertoniya Xəstəliyi Olan Pasiyentlərdə Miokard İşemiyasının Proqnozlaşdırıcısı Kimi // - Bakı: Azərbaycan Tibb Universiteti Zərifə Zeynalova 90 illik yubileyi, 2022. (həmmüəl. Quliyev F.Ə.).

11. Fibrinogenin tip 2 şəkərli diabet fonunda arterial hipertenziyalı xəstələrdə miokard işemiyasının inkişafında bir genetik amil kimi rolu // Bakı: AzDHTİ Ümummilli lider Heydər Əliyevin 100 illik yubileyinə həsr olunmuş beynəlxalq elmi-praktik konfrans, 2023

12. ITGA2 İntegrine Gene Polymorphism İn Patients With Hypertension And İschemic Heart Disease İn Azerbaijan // - Praga: European Journal of Heart Failure ESC- Heart Failure, 2023, N25 (S.2),- p.437. (həmmüəl. Quliyev F.Ə.).

13. Ассоциация полиморфизма гена фибриногена с показателями интервала Q-T у пациентов с артериальной гипертензией и сахарным диабетом 2 типа // - Россия: Эндокринология: новости, мнения, обучение, 2023, N2 (36-40).

14. Arterial hipertenziyalı xəstələrdə β-fibrinogen G/A-455 geni polimorfizminin lipid mübadiləsi göstəriciləri ilə assosiasiyası //- Bakı: Azərbaycan Tibb Jurnalı, 2023, N3, - s. 75-80. (həmmüəl. Quliyev F.Ə., T.V.Mehdiyev).

15. Ürəyin işemik xəstəliyi, tip 2 şəkərli diabetli və arterial hipertenziyalı xəstələrdə FGB genin polimorfizminin trombosit indeksləri ilə əlaqəsinin öyrənilməsi // - Bakı: Tibb və Elm, 2023, N2,(32) – s.73-78

16. Arterial hipertenziyanın müxtəlif fenotiplərində inteqrin və fibrinogen genlərinin polimorfizmi // - Bakı: Tibb və Elm jurnalı, 2023, N-4 (34) – s. 94-97 (həmmüəl. Quliyev F.Ə., İ.A.Qafarov).

17. Arterial hipertenziyalı xəstələrdə ürəyin işemik xəstəliyinin inkişafının proqnozlaşdırıcısı kimi inteqrin a2, b3 və fibrinogen genlərinin polimorfizmi // - Bakı: Metabolizma jurnal, 2023, N-4 (20) – s. 44-54

LIST OF ABBREVIATIONS

AH	arterial hypertension
AI	atherogenic index
AP	arterial pressure
CAG	coronary angiography
CVD	cardiovascular diseases
T2DM	type 2 diabetes mellitus
ECG	electrocardiography
EASD	european association for the study of diabetes
ESC	european society of cardiology
GWAS	genome-wide association study
HDL	high-density lipoprotein
IHD	ischemic heart disease
IVSt	interventricular septal thickness
LDL	low-density lipoproteins
LVPWT	left ventricular posterior wall thickness
SNP	single nucleotide polymorphism
TC	total cholesterol
TG	triglycerides
TTE	echocardiography
VLDL	very low-density lipoproteins

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