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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

STUDY OF APOPTOSIS BIOMARKERS IN RISK GROUPS OF ISCHEMIC HEART DISEASE

Specialty: 2406.02 – " Biochemistry”

Field of Science: Medicine

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GENERAL CHARACTERISTICS OF RESEARH WORK

Relevance of the research topic. Ischemic heart disease (IHD) is deemed as one of the most pressing problems in modern medicine[1]. IHD and arterial hypertension (AH) can lead to chronic heart failure (CHF). These diseases are widespread pathologies, are characterized by metabolic disorders and are more prevalent in patients with type 2 diabetes mellitus (DM-2).[2] In recent years, the relationship between metabolic disorders, including obesity and cardiovascular complications, has been widely studied. A number of risk factors for cardiovascular disease are combined in the concept of metabolic syndrome (MS). Metabolic changes during MS may lead to structural and functional disorders of the myocardium and blood vessels[3].

Statistical data point to the presence of correlation between MS and heart failure.[4] According to research conducted by Hyun Ju Yoon, drugs used in the treatment of heart failure cause impaired insulin sensitivity.[5] Moreover, treatment of MS affects the clinical course of heart failure.

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[1] Braunwald, E. Heart failure // JACC. Heart Failure, – 2013, Feb; 1 (1), – p. 1-20. doi: 10.1016/j.jchf.2012.10.002.

[2]Драпкина, О.М., Дадаева, В. А. Жесткость сосудистой стенки при хронической сердечной недостаточности // Клиницист, – 2013, № 7 (3-4), – с. 27-30. doi: 10. 17650/ 1818-8338-2013-3-4-27-3.

[3]Зятенкова, Е.В. Особенности клинического течения хронической сердечной недостаточности у пациентов с метаболическим синдромом: / автореферат диссертации на соискание ученой степени кандидата медицинских наук / – Москва, 2016.

[4]Eckel, R.H., Grundy, S.M., Zimmet, P.Z. The metabolic syndrome / // Lancet, – 2005. Apr; 365 (9468), – p. 1415-1428. doi: 10.1016/S0140-6736(05)66378-7.

[5]Jo, S-H., Kang S.M., Yoo B.S. et al. A Prospective Randomized, Double-Blind, Multi-Center, Phase III Clinical Trial Evaluating the Efficacy and Safety of Olmesartan/Amlodipine plus Rosuvastatin Combination Treatment in Patients with Concomitant Hypertension and Dyslipidemia: A LEISURE Study // J.Clin.Med. 2022, vol. 11, Issue 2, 350-363. https://doi.org/10.3390/jcm11020350.

Above-mentioned factors can lead to heart failure. According to data from the World Health Organization (WHO), the number of DM patients in the world in 2000 reached 151 million, and this figure is nowadays growing rapidly. Experts estimate that by 2025 the number of DM patients will reach 300 million. Recent studies confirm that the combination of DM-2 and IHD is an unfavorable prognosis for patients.[6]

Oxidative stress plays an important role in the development of IHD and DM-2. Free radicals are involved in the mechanisms of apoptosis and the aging process of the body, activate transcription factors, carry out the transmission of hormonal and cellular signals[7]. Free radicals cause endothelial dysfunction, which plays an important role in the pathogenesis of DM and IHD. The increase in free radicals leads to a weakening of the activity of the components of the antioxidant defense system (ADS) in the body. Oxidative stress, at the same time, accelerates the apoptosis of cardiomyocytes. In this regard, the study of oxidative stress and apoptosis in patients with IHD, DM-2 and MS is of great scientific and practical importance.

One of the mechanisms of apoptosis is implemented through the Fas-R (Fas-L) system. Activation of Fas- induced apoptosis may lead to the destruction of cardiomyocytes.[8]

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[6]Boudina, S., Abel, E.D. Diabetic cardiomyopathy, causes and effects // Reviews in Endocrine & Metabolic Disorders, – 2010, Mar; 11 (1), – p. 31-39. DOI: 10.1007/s11154-010-9131-7.

[7]Yordanova, M.G. Research of Oxidative Stress and Serum Thiols as a Criterion for the Antioxidant Barrier in Patients with Heart Failure (NYHA FC III-IV) Volume 4 – Issue 1, 2020 ISSN: 2693-4965 DOI: 10.33552/OJCR.2020.04.000578

[8] Fertin, M., Bauters A., Pinet F. et al. Usefulness of circulating biomarkers for the prediction of left ventricular remodeling after myocardial infraction // Journal of cardiology, – 2012.60(2), – p. 93-97. doi: 10.1016/j.amjcard. 2012.02. 069.

These two proteins combine to induce apoptosis. Academic literature contains sufficient information on the role of endothelial dysfunction in the course of IHD.

Vasoconstrictors (endothelin-1, etc.) and vasodilators (nitric oxide) play an important role in the development of endothelial dysfunction.[9] Recently, special attention has been paid to the role of cystatin C in endothelial dysfunction. [10] Cystatin C is not only a modern marker in the initial diagnosis of kidney damage, but also seen as a factor of atherogenesis[11].

The study of the mechanisms of apoptosis factors (apoptosis-inducing factor (AIF) and granzyme B) and oxidative stress (nitric oxide and antioxidant-thiol groups) remains relevant during IHD. In parallel, cystatin C and endothelin-1 are important markers in determining the degree of endothelial damage in patients with IHD.

These two proteins combine to induce apoptosis. Academic literature contains sufficient information on the role of endothelial dysfunction in the course of IHD.

Recent literature suggests that although some progress has been made in the study of apoptosis and oxidative stress, their role in the mechanisms of cardiomyocyte destruction during IHD has not been adequately studied. These arguments justify the goals and objectives of the dissertation.

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[9]Лапшина, Л.А., Кравчун П.Г., Титова А.Ю. и др. Значение определения нитритов-нитратов как маркеров дисфункции эндотелия при сердечно-сосудистой патологии // Український медичний часопис, – Киев: – 2009. № 6, – с. 49-53.

[10]Кузнецова, Т.Е., Боровкова, Н.Ю. Цистатин С в диагностике хронической болезни почек у больных с хронической сердечной недостаточностью в клинической практике // Архивъ внутренней медицины. 2014; (6): 38-41.

[11]Шафранская, К.С., Кашталап, В.В., Кузьмина, А.А. Роль цистатина С в прогнозировании риска развития неблагоприятных исходов коронарного шунтирования в госпитальном периоде // – Москва: Российский кардиологический журнал, – 2013, № 3 (101), – с. 45-50. DOI: 10.15829/1560-4071-2013-3-45-50.

The purpose of the research. To determine antioxidant defense indicators in blood serum of patients with IHD and risk groups of MS and DM-2, along with the study of factors of endothelial dysfunction (endothelin-1 and cystatin C) and apoptosis factors (granzyme B and AIF), as well as to define relations between these indicators.

Research objectives:

1. Determination of some biochemical parameters (lipid spectrum, glucose, glycohemoglobin, insulin, protein and albumin) in the blood of patients with IHD, DM-2, and IHD with MS;
2. To study the status of thiol, an important component of NO and ADS, which is a biomarker of oxidative stress, in the blood of patients with IHD, DM-2, and IHD with MS;
3. Study of the amount of endotelin-1 and cystatin C in the blood of patients with IHD, DM-2, IHD with MS which reflect endothelial dysfunction;
4. Determination of the level of apoptosis factors (AIF and granzyme B) in the blood of patients with IHD, DM-2, IHD with MS;
5. To determine the correlation between indicators of oxidative stress and apoptosis factors in the studied patient groups.

Research methods. Biochemical and immunoenzyme analysis methods were applied in the research.

The main provisions of the dissertation:

- Increased levels of nitric oxide (NO) and decreased thiol status are important factors in the formation of the clinical course of IHD.
- Increased serum levels of endothelin-1 and cystatin C in patients with MS and DN-2 with IHD, who belong to the IHD and risk group, indicate severe endothelial dysfunction and worsening of the clinical course of the disease.
- Determination of apoptosis factors (granzyme B and AIF) in the blood serum of patients with MS with DM-2 belonging to the risk group is of prognostic importance in the development of IHD.

- The study of the interaction between the indicators of the antioxidant defense system of oxidative stress and apoptosis factors determines the pathogenetic mechanisms of the development of IHD in risk groups.

Scientific novelty of the research:

1. The study revealed that the process of apoptosis is activated during IHD and in risk groups of this pathology. In this case, the degree of induction of apoptosis reflects the severity of the clinical course of the disease.

2. For the first time, a correlation was found between the structural and functional state of the heart and apoptosis markers (granzyme B and AIF) and oxidative stress indicators (thiol status, NO). This confirms their participation in the process of destruction of cardiomyocytes.

3. The concentration of cystatin C in the blood serum during IHD determines the severity of the process of atherosclerosis.

4. At the same time, the functional activity of the endothelium was studied, and the relationship between the indicators of oxidative stress (nitric oxide) and endothelin-1 was revealed.

Practical dalue of the research:

Determination of apoptosis markers (granzyme B and AIF), endothelin-1 vasoconstrictor and nitric oxide vasodilator in the blood serum of patients with IHD allows to objectively assess the severity of circulatory disorders.

An increase in the concentration of granzyme B, AIF, endothelin-1 and NO in the blood serum, and a decrease in thiol status, may further deepen the development of IHD in risk groups such as MS and DM-2.

Object and subject of research. Blood samples from 114 patients who applied to the Teaching Clinical Biochemistry Laboratory of the Azerbaijan Medical University were used in the study. Among these patients, 39 had IHD, 41 had IHD with DM-2, and 34 were found to have IHD along with MS.

Approbation of research work. Materials of the dissertation were discussed at the VII conference of the National Research Institute of

Medical Prevention named after Akhundov "Actual problems of medical prevention in the XXI century: Achievements and prospects" (Baku, 2014), Qafqaz University. II International Scientific Conference of Young Researchers (Baku, 2015), at the scientific-practical conference held at AMU on the occasion of the 120th anniversary of A.Aliyev (Baku, 2017), Acad. International Scientific-Practical Conference dedicated to the 96th anniversary of Z.Aliyeva (Baku, 2018), International Scientific Conference on bioorganic chemistry "XII readings in memory of acad. Yu.A. Ovchinnikova", Scientific proceedings of VIII Russian Symposium "Proteins and peptides" (Moscow, 2017), "Public Health and Health", at the scientific conference dedicated to the 75th anniversary of A. T. Agayev (Baku, 2019), Proceedings of 2nd International conference one health problems & solutions. Discussed at Khazar University (Baku, 2019) and other International Symposiums and Conferences.

Application of research results in practice. The results of the research were applied in the curriculum of the Department of Biochemistry.

Published works. 19 scientific works on the topic of the dissertation - 3 articles, 7 theses were published in the republic, 4 articles and 5 theses were published in foreign journals.

The organization where the dissertation work is carried out. The dissertation work was performed at the Department of Biochemistry of Azerbaijan Medical University and the Teaching Clinical Biochemistry Laboratory of AMU.

Volume and structure of the dissertation. The dissertation consists of 162 computer pages. Introduction to the dissertation (8674), literature review (48968), chapter II on research materials and methods (30888), chapter III covering research (62365), discussion of the obtained results (51766), results (1545), practical recommendations (443), consists of sections with 204649 characters. The list of literature refers to 252 scientific sources (16 of them in Azerbaijani, 105 in Russian and 133 in foreign languages). The dissertation is illustrated with 19 tables, 4 pictures and 16 graphs.

Chapter 1 is dedictaed to the review of the literature on the role of apoptosis and oxidative stress in the pathogenesis of the disease in patients with ischemic heart disease, type 2 diabetes and metabolic syndrome.

MATERIALS AND METHODS OF RESEARCH

Blood samples from 114 patients who applied to the Teaching Clinical Biochemistry Laboratory of the Azerbaijan Medical University were used in the study. The control group consisted of 20 practically healthy individuals. Among patients, 52 were female and 62 were male.

Patients were divided into 3 groups: Group I - 39 patients with IHD; average age range was 56.15 ± 1.02 (min - 45, max - 69); Group II - 41 patients with IHD along with DM-2; average age range was 56.44 ± 1.18 (min - 41, max - 69); Group III - 34 patients with MS along with IHD; average age range was 54.50 ± 1.32 (min - 40, max - 69).

Biochemical research methods. In the study, the concentration of biochemical indicators in the blood plasma of patients and healthy individuals was determined using the appropriate reagent kits. Biochemical indicators included TCL, HDL CL, LDL CL, TG, glucose, glycosylated hemoglobin, insulin, albumin, total protein. The level of these parameters was analyzed with a semi-automatic Mindray BA-88A analyzer.

To assess the degree of atherosclerotic damage in the examined groups of patients, the following indicators of lipid metabolism were studied: total cholesterol, high-density lipoprotein cholesterol (HDL CHL), low-density lipoprotein cholesterol (LDL CHL), triglycerides. Based on the obtained data, the atherogenicity coefficient (AV) was calculated by the following formula: (TC - HDL CL) / HDL CL.

To assess the degree of atherosclerotic damage in the examined groups of patients, the following indicators of lipid metabolism were studied: total cholesterol, high-density lipoprotein cholesterol (HDL

CL), low-density lipoprotein cholesterol (LDL CL), triglycerides.[12] Based on the obtained data, the atherogenicity coefficient (AC) was calculated by the following formula: (XS - HDL CL) / HDL CL.

The principle of the method is based on the determination of cholesterol by enzymatic method (cholesterol-esterase enzyme).

Determination of serum glucose. The amount of glucose, a marker of diabetes mellitus, was determined by the method of enzymatic gluoxidase.

Determination of glycosylated hemoglobin in the blood. The level of glycosylated hemoglobin was determined by colorimetric combination in erythrocytes - thiobarbituric acid.[13]

The determination of NO (nitric oxide) is based on the conversion of nitrate to nitrite in the presence of the enzyme nitrate reductase. The concentration of nitrite is determined colometrically by the azo dye formed by the Griss reaction.

The amount of endothelin-1 and cystatin C in the blood serum, indicators of vascular endothelial status, and biomarkers of apoptosis granzyme B and apoptosis-inducing factor (AIF) were determined by IFA method. Quantitative analysis of NO was pefromed with R&D Systems reagent kit. The status of thiol, an indicator of the antioxidant system, was studied with the help of a commercial reagent kit from Immundiagnostic company. This method uses the method of immunoenzyme competitive inhibition.

Insulin Resistance Index (HOMA-IR) for all patients with metabolic syndrome was calculated with formula

$$\frac{glucose\ mmol/l\ x\ insulin}{22{,}5}.$$

[12]Колб, В.Г., Камышников, В.С. Справочник по клинической химии (2-ое издание). – Минск: «БелаРусь», – 1982. – 367 с.

[13]Əfəndiyev, A.M., Islamzadə F.Q., Qarayev, A.N., Eyyubova A.Ə. Bioloji kimyadan laboratoriya məşğələləri (dərs vəsaiti) – Bakı: – 2015. – 376 s.

All data obtained during the study was statistically analyzed, taking into account modern recommendations. The indicators in the groups are arranged in a series of variations, and for each variation series, the average value of the indicator (M), the standard error of this indicator (m), the minimum (min) and the maximum (max) values are calculated.

A non-parametric method - Wilcoxon (Mann-Whitney) criterion (U) was used to determine the difference between the indicators in the groups.

RESULTS AND THEIR DISCUSSION

In the studied groups, the patients were divided according to age, duration of illness and body mass index (BMI).

Control group included healthy people of both genders - 11 men and 9 women. This, in turn, accounted for 55% of men and 45% of women. Their age range was between 41-70, the average age was 54.70 ± 2.09. The confidence interval was between (50.32-59.08). Body mass index was 23.55 ± 0.80; the confidence interval was between (21.86-25.24).

Of the 39 patients in the IHD group, 22 were men and 17 were women. In percentage terms, this was 56.4% and 43.6%, respectively. Their age range was 45-69 years, and the average age was 56.15 ± 1.02 years. The confidence interval was between (54.09-58.22). The average duration of the disease was 12.56 ± 0.56 years.

The confidence interval was between (11.44-13.69). Body mass index was 24.86 ± 0.64 and did not differ significantly from the control group.

In the second group of patients (IHD with DM-2), the number of men was 22 people (53.7%) as in the first group of patients, and women were 19 patients (46.3%). Their age range was between 41-69, with an average age of 56.44 ± 1.18. The confidence interval was between (54.05-58.82). The mean duration of the disease was 12.44 ± 0.54 years; the confidence interval was between (11.35-13.53). Body

mass index was 25.99 ± 0.67 and did not differ from the control group; the confidence interval was between (24.63-27.35).

The number of patients in the third group was 18 men (52.9%) and 16 women (47.1%). Their age range was between 40-69, with an average age of 54.50 ± 1.33. The confidence interval was between (51.81-57.19). The average duration of the disease was 8.03 ± 2.18 years; the confidence interval was between (7.27-8.79). In total, blood plasma was obtained from 73 men (54.5%) and 61 women (45.5%) during the study. Their age range was between 40-70, the average age was 55.60 ± 0.65. The confidence interval was between (54.32-56.89). The mean duration of the disease was 11.17 ± 0.35 years; confidence interval (10.48-11.86). The mean body mass index was between 27.83 ± 0.55 and the confidence interval (26.75-28.92).

20 of the DM patients were treated with substitute medicine and 21 were insulin users.

Relevant analyzes were performed by taking blood from a vein on an empty stomach from patients included in the research and control group.

The average figure of group IHD-BMI is 24.85 ± 0.63 (min - 19.4; max - 31.1); in II group IHD with DM-2 average figure for BMI was 25,99 ± 0,67 (min - 19,0; max - 36,2); in III group with IHD and MS - average figure of BMI was 35.98 ± 0.76 (min - 27.4; max - 46.4)

Studies have shown that oxidative stress and apoptosis process are interrelated during diabetes mellitus, IHD, and metabolic syndrome. Thus, the changes that occur directly affect the process of apoptosis. When lipids are excreted as a result of apoptosis, they accumulate in the vessel wall and lead to thickening of the connective tissue, which eventually results in the development of atherosclerosis.

Hypercholesterolemia, hypertriglyceridemia, and, in parallel, a sharp decrease in the concentration of HDL CHL were observed in the studied groups. According to the results of the study, in patients with IHD, the concentration of TCL increased by 58.1% ($p < 0.001$), the concentration of TG - by 3.7 times ($p < 0.001$), the concentration

of LDL CHL – by 63.1% ($p < 0.001$)) with statistically significantly increase compared to the control group, while the concentration of HDL CHL by contrast decreased by 35.6% ($p < 0.001$).

The atherogenicity index in the first group of patients was (4.81-0.831) / 0.831 = 4.79. In this group of patients, the process of atherosclerosis develops and can lead to aggravation of the disease. This trend has been exacerbated in patients with IHD and DM. There is a 2.3-fold increase in NO in blood plasma, a 29.5% decrease in thiol groups, and a 2-fold increase in ET-1. In patients with metabolic syndrome, the intensity of OS processes is observed and, in this connection, affects the above-mentioned parameters. Thus, the amount of NO increases up to by 106.86%. It also leads to a decrease in thiol status to 21.1%, an increase in endothelium-by to 47.4% and an intensity of apoptosis. Correlation analysis between NO and thiol status and endothelium-1, which are indicators of the intensity of OS processes, shows a positive correlation.

As a result of conducted experiments, the thiol status was determined from the ADS system indicators. The average value of thiol status was 432.9 ± 8.6. The minimum value for this indicator within the group is 314.7; the maximum value is 494.0; The confidence interval was set at 415.4-450.3. Compared to the control group, this indicator decreased by 14.7% at $p < 0.001$. In the majority of patients in this group (36 people, 92.3%), the indicator of thiol status was lower than in the control group, and in 3 people this indicator did not differ from the control group.

Dynamics of changes in the values of cystatin C and Et-1 for this group of patients were as follows. The mean value observed for cystatin C within the group was 1,267 ± 0.103 mg / l, the minimum value was 0.64 mg / l, the maximum value was 2.97 mg / l, and the confidence interval was 1,054-1.48 mg / l. This is 135.9% (2.4 times) more than in the control group. In this group, the calculated p for cystatin C is <0.001. Of the 24 patients examined, 15 patients (62.5%) had cystatin C levels above normal, and 9 patients (37.5%) had normal levels.

Cystatin C has been shown to be a potent and independent predictor of cardiac death in patients with severe or severe renal impairment.[14] In such cases, cystatin C is expected to significantly improve risk stratification in patients with acute heart failure.

The observed values for Et-1 are as follows. The mean value was 10.06 ± 0.27 ng / ml. Compared to the control group, the increase rate was 69.7% (1.7 times), and the significancy was determined at p <0.001. Out of 24 values obtained in this group, 2 values (8.3%) did not change compared to the control group, and 22 values (91.7%) increased.[15]

The mean value for AIF in this group of patients was 1.64 ± 0.16 pg / ml, which is 73.7% (1.7 times) higher than in the control group. Within this group, the minimum value is 0.2 pg / ml and the maximum value is 3.2 pg / ml; the confidence interval was 1.32-1.96 pg / ml. The calculated accuracy was p <0.01. The AIF concentration was below normal in only 1 patient (4.2%) out of the 24 patients in this group. In 14 people (58.3%) this indicator did not change compared to the control, and in 9 people (37.5%) the AMF concentration decreased (Figure 1).

The mean value for Granzyme B was 22.0 ± 1.0 pg / ml, which is 51.9% (1.5 times) higher than the value in the control group. The calculated accuracy was p <0.001. In 15 patients out of 24 patients (62.5%) this indicator was above the control, and in 9 people (37.5%) it was within the norm (Figure 2).

[14.] Mammadova F.İ., Efendiyev A.M., Azizova G.İ., Dadashova A.R.. Cyctatin C as a predictor of complications in chronic heart failure / Proceedings 2nd International conference one health problems &solutions. Khazar University Baku, Azerbaijan 24-25 may 2019, p. 92-93.

[15.] Мамедова Ф.И., Дадашова А.Р., Гусейнова Э.Э., Азизова Г.И. Дисфункция эндотелия у больных с хронической сердечной недостаточностью при метаболическом синдроме и сахарном диабете типа 2 / "İctimai sağlamlıq və Səhiyyə" t.e.d. Ə.T. Ağayevin anadan olmasının 75 illiyinə həsr edilmiş elmi konfransın materialları, Bakı, 2019, VI c. 513-516.

Biochemical parameters of patients with IHD and DM-2

Lipidogram, carbohydrate, OS, ADS system and apoptosis factors and indicators of endothelial dysfunction were determined for the group of patients with IHD with DM-2 as in the previous group. If we look at the established lipidogram indicators, we see a change in the increase in all indicators in patients with SD-2. Comparison of values in this group of patients with control group reveals the following results. In patients with DM-2, the concentration of TCL increased by 81% ($p<0.001$), the density of TG – by 4.6 times ($p<0.001$), the concentration of LDL CHL – by 44.9% ($p<0.001$) compared to the control group, while the density of HDL CHL decreased by 36.3% ($p<0.001$). The atherogenicity index in this group was 5.40.

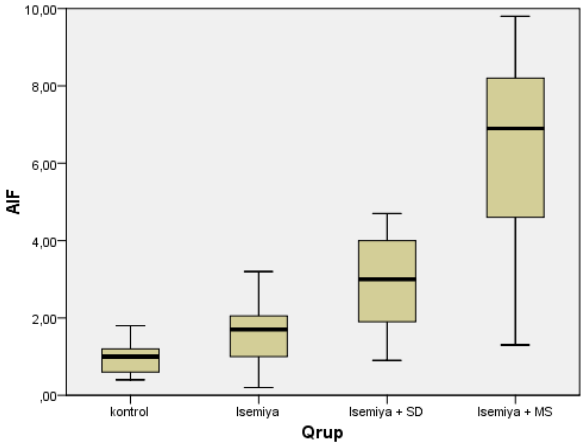

Figure 1. Changes in AIF concentration in control group, patients with IHD, IHD with DM-2 and with MS

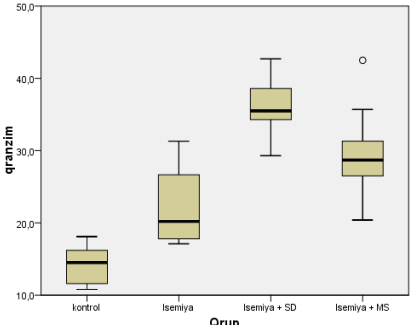

Figure 1. Changes in Granzyme B concentration in control group, patients with IHD, IHD with DM-2 and with MS

The mean value of CHL is 4.51 ± 0.09 mmol / l in group I, and in group II this figure increases to 5.25 ± 0.24 mmol / l (1.2 times). Compared to the control group, this figure increases by 1.8 times. The calculated stastifical significance was p <0.001.

The following trend is observed in the amount of TG: the mean value is 4.66 ± 0.16 mmol / l, an increase of 1.2 times compared to group I (in group I it was 3.74 ± 0.16 mmol / l), and 4,6 times increase compared to the control group (1.01 ± 0.09 mmol / l in the control group). The confidence interval is 4.34-4.97 mmol / l. The stastifical significance was p <0.001. In all patients examined (41 people, 100%), the amount of TG was above normal level. Compared to the first group, it decreases by 1.1%. The confidence interval was set at 0.4-1.8 mmol / l. The mean value of LDL CHL was 3.61 ± 0.16 mmol / l.

It was found that structural disorders of cardiomyocytes are associated with increased LPO processes in patients with DM and MS, and this process plays an important role in the pathogenesis of the disease. The results of the study show that there is a negative correlation between the amount of TS and NO, an indicator of the antioxidant system (ADS), and a decrease of 14.67% of TS in the group of patients with IHD and 29.5% in patients with IHD with DM-2. This fact indicates the weakening of the protective power of ADS

and the formation of reactive thiol radicals. In turn, the above changes cause endothelial damage.

Table 1

Oxidative stress, ADS, indicators of endothelial dysfunction, biomarkers of apoptosis in patients with IHD and DM-2

Indicators	Control group, n=20	Patients group, n=26	p (Mann-Uitni) criterion (U)
NO, mcmol/l	10,2±0,3 (9,6-10,8)	23,4±0,4 (22,5-24,2)	0,000
Thiol status	507,3±1,9 (503,4-511,2)	357,7±5,3 (347,0-368,5)	0,000
Cystatyn C, mg/l	0,537±0,048 (0,433-0,642)	1,246±0,029 (1,186-1,305)	0,000
Endotelin-1, pg /l	5,93±0,45 (4,96-6,89)	11,82±0,25 (11,30-12,33)	0,000
AİF, pg/ml	0,94±0,11 (0,7-1,18)	2,99±0,21 (2,55-3,43)	0,000
Granzyme B, ng/ml	14,5±0,7 (13,0-16,0)	36,4±0,7 (35,0-37,8)	0,001

Changes in oxidative stress, AOS, cystatin C and endothelin-1 were studied in this group of patients.

The mean value for NO in the group with IHD and DM-2 was 23.4 ± 0.4 μmol / l. Compared to the control group, this indicator increased by 129% (2.3 times). Compared to patients with IHD, it is 1.7 times higher ($p < 0.001$).

As a result of the experiments, the amount of thiol status was determined from the indicators of the ADS system. The results reveal that the mean value of thiol status was 357.7 ± 5.3. Compared to the control group, this figure decreased by 29.5%. Comparing patients with IHD, a decrease of 17.4% is observed ($p < 0.001$).

In all patients in this group (100%), thiol status did not change

relative to the control group.

Cystatin C and endothelin-1 were detected in blood plasma to achieve the goal of the study.

The mean value observed within the group for cystatin C was 1,246 ± 0.029 mg / l. This is 131.9% (2.3 times) more than in the control group. Compared to group I, this figure decreased by 1.7%. ($p < 0.001$).

Compared with the control group, there was an increase of 99.3% (2 times) and by 17.5% in patietns with IHD in and Et-1 ($p < 0.001$).

Simultaneous occurrence of diabetes mellitus in people with CVD complicates the clinical course of the disease, which accelerates the process of oxidative stress and apoptosis. Taking this into account, in our study we analyzed the amount of AIF and granzyme B in the blood plasma.

The mean value for AIF in this group of patients was 2.99 ± 0.21 pg / ml, which is 217% (3.2 times) higher than the value in the control group ($p < 0.001$).

The mean value for Granzyme B was 36.4 ± 0.7 pg / ml, which is 151.1% (2.5 times) higher than the value in the control group ($p < 0.001$).

Comparing the two groups (IHD and IHD and DM-2), it appears that these two indicators increase more sharply in patients with DM-2: AIF by 82.5% (1.9 times), and granzyme B by 65.3% (1, 7 times), $p < 0.001$.

It has been shown that loss of mitochondrial membrane integrity and separation of apoptotic factors are the main stages of the signal cascade, leading to the death of neurons during various neurological disorders, including ischemic injury. According to new data, mitochondrial factor, which induces apoptosis, translocates the nucleus and stimulates cell death independent of caspase as a result of glutamate toxicity, oxidative stress, hypoxia or ischemia.

Therefore, the results we obtained show that the process of apoptosis is accelerated in patients with IHD as a result of the intensity of

oxidative stress LPO. These processes lead to the death of cardiomyocytes, which in turn leads to aggravation of the disease.

In addition to IHD and DN-2, a correlation was found between the indicators in the group of patients with IHD. A negative correlation was found between total cholesterol and thiol status ($r = -0.319$; $p < 0.05$), and a positive correlation was found between total cholesterol and Granzyme B ($r = + 0.415$; $p < 0.05$). There was a negative correlation between triglycerides and cystatin C ($r = -0.501$; $p < 0.01$). There was a positive correlation between TS and endothelin-1 ($r = + 0.528$; $p < 0.01$). There is a positive correlation between total protein and albumin ($r = + 0.563$; $p < 0.01$). A positive correlation ($r = + 0.457$; $p < 0.05$) was observed between NO and granzyme B. In addition, a negative correlation was found between LDL CHL and body mass index ($r = -0.349$; $p < 0.05$), NO and disease duration ($r = -0.426$; $p < 0.05$).

Biochemical parameters of patients with IHD and MS

Lipidogram, carbohydrate, OS, ADS system and apoptosis factors for the group of patients with IHD and MS, as in the previous two groups and indicators of endothelial dysfunction were determined. In patients with MS, the concentration of TCHL increased by 94.9% ($p < 0.001$), TG -by 4.2 times ($p < 0.05$), LDL CHL – by 95.4% ($p < 0.001$)) and the density of HDL CHL decreased by 2.5 times ($p < 0.001$). The atherogenicity index is 9.8. The value obtained for the control group has changed almost to the same extent as in the previous two groups (IHD and IHD with DM-2) compared to the control group. The mean value for this group of patients (IHD and MS) was 5.55 ± 0.21 mmol / l ($p < 0.001$).

The CHL LP classes vary as follows: The mean value of the HDL CHL is 0.515 ± 0.026 mmol / l, which is a 60.1% decrease compared to the control group (1.29 ± 0.111 mmol / l in the control group), $p < 0.001$.

LDL CHL level is 4.87 ± 0.14 mmol / l, which means an increase of 95.7% (2 times) compared to the control group (2.49 ± 0.14 mmol / l in the control group) ($p < 0.001$) .

AC (5.55-0.51) / 0.51 = 9.88 in patients with IHD and MS. In this group, the tendency to increase AC occurs more rapidly, and it can be said that it is the most likely complication of the disease among the risk groups.

For TG, an increase was observed as in both of the above groups. Thus, the mean value obtained in patients with IHD and MS was 4.26 ± 0.20 mmol / l. Compared to the control group, the observed increase is more pronounced - 322.2% (4.2 times) ($p < 0.05$).

In our study, hypercholesterolemia, hypertriglyceridemia, and, in parallel, a sharp decrease in HDL CHL were observed in the patients studied. For example, in patients with MS, a 1.9-fold increase ($p < 0.001$) and a 4.2-fold increase in TG ($p < 0.05$) occurred in patients with MS, while a 2.5-fold decrease in HDL CHL ($p < 0.001$) was observed.

Thus, dyslipidemia was found in the studied patients. The term dyslipidemia more accurately describes the disruption of lipid metabolism in MS. At the same time, triglycerides containing apo-B increase the cholesterol of very low-density lipoproteins (LDLs), small, dense particles of LDL cholesterol, and decrease the cholesterol particles of high-density lipoproteins (HDLs) containing apo-A1. These disorders have a certain sequence or chain of pathogenic development. During insulin resistance, lipolysis occurs in the fat cell, which leads to the entry of large amounts of free fatty acids into the bloodstream through the portal vein. They are the substrate for the synthesis of triglycerides and very low-density lipoproteins (LDLs) in the liver. Under the influence of hepatic lipase, CASLP is converted into small and dense particles of low-density lipoproteins. Such particles rapidly oxidize and enter the sub-endothelial phase. As a result, the process of atherosclerotic damage develops. At the same time, an increase in the activity of the protein that carries cholesterol esters leads to the transition of triglycerides from CASLP to ASLP

(instead of cholesterol). As a result, the concentration of the main particles that carry out the reverse transport of cholesterol - HDLs - decreases. In addition, there is a qualitative change in these particles (smaller particles), which leads to their rapid removal from the bloodstream. Thus, disruption of lipid metabolism in MS leads to a violation of the ratio between "bad" (LDL CHL and CASLP CHL) and "good" (HDL CHL a) cholesterol, as well as an increase in the concentration of triglycerides differs by. In practical medicine, these disorders are called lipid triads.

The parameters determined from the carbohydrate parameters were glucose and HbAlc. The increase in glucose was 52% (1.5 times) (6.16 ± 0.12 mmol / l), p <0.001.

HbAlc is closer to the value for healthy people. Thus, the value obtained in the control group was 5.75 ± 0.08%, and the value obtained in patients with IHD and MS was 5.57 ± 0.13%. No difference in HbAlc relative to the control group was identified.[16]

The accepted norm for total protein is 65-85 g / l. No significant changes were observed in this indicator with the UHD and MS. There were no changes compared with the control group, indicating that there were no significant changes in total protein levels in patients with MS.

For albumins, the main protein fraction of blood plasma, a downward trend was observed. The mean value for the studied parameter was 44.3 ± 1.1 g / l. A 7.6% decrease was observed compared to the control group (p <0.05).

The level of albumin, one of the parameters of protein metabolism, does not change between groups ($\chi 2$ = 4,357; df = 3; p = 0.225). The total amount of protein varies statistically ($\chi 2$ = 74,320; df = 3; p <0.0001).

Changes in oxidative stress, ADS, cystatin C, and endothelin-1 in this group of patients are presented in the following table (Table 2).

Table 2

Oxidative stress markers, AOS, cystatin C, indicators of endothelial dysfunction and levels of apoptosis factors in patients with IHD and MS

Indicators	Control group, n=20	Patient group, n=25	p (Mann-Uitni) criterion (U)
NO, mcmol/l	10,2±0,3 (9,6-10,8)	21,1±0,7 (19,6-22,6)	<0,001
Thiol status	507,3±1,9 (503,4-511,2)	400,2±6,7 (386,6-413,7)	<0,001
Cystatin C, mg/l	0,537±0,048 (0,433-0,642)	1,191 ±0,042 (1,104-1,278)	<0,001
Endotelin-1, nq/l	5,93±0,45 (4,96-6,89)	8,74±0,25 (8,22-9,25)	<0,001
AIF, pq/ml	0,94±0,11 (0,7-1,18)	6,35±0,47 (5,37-7,33)	<0,001
Granzyme B, pq/ml	14,5±0,7 (13,0-16,0)	28,7±1,0 (26,7-30,8)	<0,001

Patients in this group found the following changes of oxidative stress, AOC, cystatin C, and endothelin-1.

Particular interest is drawn to change in the ADS system status against the background of changes in OS variables (NO). As a result of experiments the mean value of NO was 21,1±0.7 mcmol / l.[16] Compared with the control group this indicator increased by 107% (2,1-fold) (p <0.001).

A comparison of the two groups of patients showed that the above parameters increased equally in group III, for example, in group I patients the NO increased to 13.7 μmol / l (10.2 μmol / l in the control group). In patients with DM-2, this figure rises to 23.4 μmol / l.

[16]Mammadova F.İ., Azizova G.İ. Dadashova A.R. Markers of apoptosis and oxidative stress in congestive heart failure // The Moldovan Medical Journal, February 2017, Vol. 60, N. 1, p. 22-25.

As for thiol status, there is a decrease in both groups (432.9 in group I; 357.7 in group II). Decreased thiol status was noted ($p < 0.001$). Apoptosis rates were higher in AIF groups I and II (287.7% and 112.4%), while granzyme B, in contrast to these groups, increased by 30.7% in group I and 20.9% in group II. The calculated accuracy was $p < 0.001$.

There is also a correlation between the indicators in the group of patients with IHD and MS.

Cystatin C and endothelin-1 were determined in the blood plasma to achieve the goal of the study. The values obtained for these parameters were as follows. The mean value observed within the group for cystatin C was 1,191 ± 0.042 mg / l. This is 121.7% (2.2 times) higher than in the control group ($p < 0.001$). Cystatin C was found to be 1,267 mg / l in group I, 1,246 mg / l in group II, and 1,191 mg / l in group III compared to the control group ($p < 0.001$). Cystatin C was determined in 25 patients with IHD and MS. The results show that in 17 of this group of patients (68.0%) the concentration of cystatin C increased compared to the control group, and in 8 people (32.0%) it was equal to the norm.

The increase in the level of Et-1 compared to the control group was found to be 47.3% (1.5 times) ($p < 0.001$).

If we compare the results obtained in the previous study with the patients of group III, we can see that the dynamics of change of these indicators is the same. For example, Et-1 in group I was 10.06 ng / l, in group II 11.82 ng / l, and in group III 8.74 ng / l.

The results of the study show that statistically significantly increased endothelin-1 ($\chi 2 = 60,028$; $df = 3$; $p < 0.0001$) may be a factor in the unfavorable prognosis.

The mean value for AIF in this group of patients was 6.35 ± 0.47 pg / ml, which is 573.3% (6.7 times) higher than in the control group.

Apoptosis va;ues of AIF were higher in groups I and II (287.7% and 112.4%), while the difference between Granzyme B and these groups was 30.7% increase in group I and 20.9% increase in group II

The mean value for Granzyme B was 28.7 ± 1.0 pq / ml, which is

98.6% (2 times) higher than the value in the control group.

The density of Granzyme B, one of the markers of the process of apoptosis, increases at a statistically significant level ($\chi 2 = 68,392$; df = 3; $p < 0.0001$). The same changes were reflected in the AIF parameter ($\chi 2 = 60,397$; df = 3; $p < 0.0001$).

Apoptosis values of AIF were higher in groups I and II (287.7% and 112.4%), while the difference between granzim B and these groups was 30.7% in group I and 20.9% in group II. The calculated accuracy was $p < 0.001$.

There is a correlation between the values determined in the group of patients with IHD and MS. A negative correlation ($r = -0.515$; $p < 0.01$) was found between triglycerides and granzyme B. Positive correlation between LDL CHL and total protein ($r = + 0.441$; $p < 0.01$). There is a positive correlation ($r = + 0.443$; $p < 0.05$) between endothelin-1 and HDL HCL. A strong positive correlation was found between AIF and granzyme B ($r = + 0.600$; $p < 0.01$). In addition, there is a negative correlation between AIF and age ($r = -0.455$; $p < 0.05$). Body mass index was positively correlated with LDL HCL ($r = + 0.371$; $p < 0.05$) and albumin ($r = + 0.356$; $p < 0.05$). In addition, a negative correlation was found between body mass index and endothelin-1 ($r = -0.523$; $p < 0.05$). In the studied groups, there was a positive correlation between the concentration of hyperglycemia TCHL ($\rho = 0.265$, $p = 0.004$) and TG ($\rho = 0.361$, $p < 0.001$), the level of glycosylated hemoglobin ($\rho = 0.223$, $p = 0.017$) with TG . At the same time, an increase in the density of HFS can lead to a decrease in thiol status ($\rho = -0.203$, $p = 0.031$), acceleration of apoptosis (between TQ and AIF - $\rho = 0.292$, $p = 0.011$). Hyperglycemia results in a weakening of AOS activity in the body, as a negative correlation between thiol status and glucose ($\rho = -0.515$, $p < 0.001$) has been identified. As thiol status decreases, NO concentrations ($\rho = -0.478$, $p < 0.001$) and granism B levels ($\rho = -0.485$, $p < 0.001$) increase significantly. In addition, an increase in glucose concentration leads to an acceleration of the expression of apoptosis factors, such as between glucose concentration and AIF ($\rho = 0.725$, $p < 0.001$) and granzim B

($\rho = 0.706$, $p < 0.001$), between glycosylated hemoglobin and granzim B. ($\rho = 0.232$, $p = 0.045$) a positive correlation was recorded. Hyperglycemia also plays an important role in endothelial damage (between glucose and endothelin-1 - $\rho = 0.357$, $p < 0.002$; between glucosylated hemoglobin and endothelin -1 - $\rho = -0.421$, $p < 0.001$). There is a positive correlation between AIF and Granzim B ($\rho = 0.293$, $p = 0.011$) and NO ($\rho = 0.386$, $p = 0.001$), and NO with Granzim B ($\rho = 0.651$, $p < 0.001$).

NO is a key player in cell regulation and plays an important role in apoptosis. Thus, in addition to regulating the tone of the cardiovascular system, NO is involved in the regulation of the inflammatory response and apoptosis. NO is formed in the endothelium, phagocytes and other cells, during the process of apoptosis leads to the formation of peroxynitrites and the formation of pores in the membrane of mitochondria, the release of cytochrome C into the cytoplasm. Hydroxyl and lipid radicals formed by the interaction of nitric oxide with peroxynitrite cause oxidation of SH groups of proteins, superoxide dismutase and inactivation of DNA ligase. The existing correlation between nitric oxide and granular B and AIF demonstrates the inductive effect of nitric oxide on apoptosis. Nitric oxide inhibits the synthesis of bcl-2 proteins, increases the permeability of mitochondria, and as a result, a large number of AFO enters the cell cytoplasm.

RESULTS

1. Concentration of TCHL in the blood of patients with IHD, IHD with DM-2, IHD with MS increased by 58.1%, 81.0% and 94.9% respectively; in TG – by 3.7 times; 4.6 times and 4.2 times; LDL HCL - 63.1%; 44.9% and 95.7% compared to the control group. In contrast the concentration of HDL CHL XS decreases by 35,6%, 36.3% and 60.1% which indicate serious disorders of lipid metabolism. These results prove that DM-2 and MS are risk factors for the development of IHD, including the complication of the clinical course of the disease [3,11,19]

2. Significant increase in NO, a biomarker of oxidative stress, was obsered in the blood of patients with IHD, IHD with DM-2, IHD and MS, by 34.3%, 2.3 times and 2.1 times, respectively; Thiol status, an important component of ADS decreased by 14.7%;, 29.5% and 21.2%, which indicates activation of oxidative stress in these patients [9,13]
3. Concentration of endothelin-1, which determines endothelial dysfunction, increased in the blood of patients with IHD, IHD and DM-2, IHD and MS, respectively, by 69.7%; 99.3% and 41.3%; the concentration of cystatin C increased by 2.4 times; 2.3 times and 2.2 times, which determines the degree of damage to the vascular endothelium [5,15,19]
4. AIF and granzyme B levels with apoptosis factors in patients with IHD increased by 73.7% and 51.9%, respectively; in patients with DMS increased by 22.3 times and 2.5 times and a significant increase in 6.7-fold and 98.6% (2.0-fold) was observed in apoptosis in patients with IHD with MS [3,9,18]
5. Positive correlations between oxidative stress and apoptosis factors were identified in the studied disease groups. Increased concentrations of Granzyme B, AIF, and NO, and decreased thiol status were more pronounced in patients with IHD along with DM-2 and MS [1,2,14]

PRACTICAL RECOMMENDATIONS

1. Determination of lipid profile, nitric oxide, thiol status, endothelin-1, cystatin C and apoptosis markers (AIF and granzyme B) is recommended in type 2 diabetes and metabolic syndrome, which are risk groups for coronary heart disease.
2. Determination of apoptosis markers (AIF and granzyme B) in ischemic heart disease can be used as highly informative tests in predicting the clinical severity of the disease and chronic heart failure.

List of published scientific works on the topic of the dissertation

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LIST OF ABBREVIATIONS

AIF	– apoptosis-inducing factor
LDL	– low density lipoproteins
MS	– metabolic syndrome
NO	– nitric oxide
TG	– triglycerides
OS	– oxidative stress
DM	– diabetes mellitus
IHD	– ischemic heart disease
CD	– cardiovascular diseases
TCHL	– total cholesterol
HDL	– high density lipoproteins
AFO	– active forms of oxygen

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