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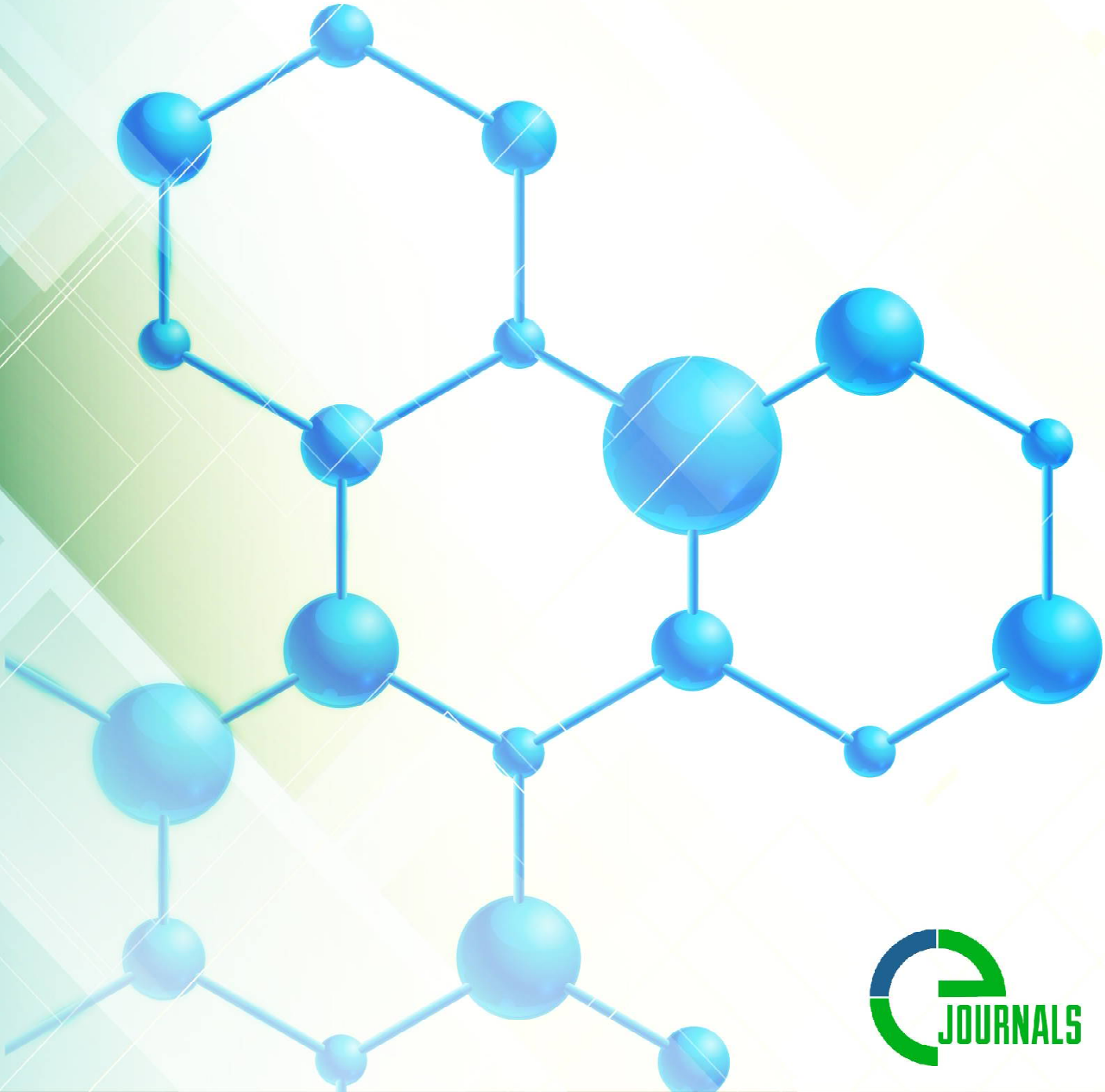

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INDICATORS OF PLATE AGGREGATION IN PATIENTS WITH MULTIVESSEL CORONARY LESIONS AND DIABETES MELLITUS

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Abstract.The results of the aggregation data in 122 patients with multivessel coronary lesions, including 67 men, 55 women (mean age 61.83 ± 19.5 years), were analyzed in this study. The patients are divided into 2 groups depending on the presence of diabetes mellitus. Thus, the study of the features of antiplatelet therapy in patients with diabetes mellitus demonstrated a significantly pronounced ADP-induced rate and degree of platelet aggregation in comparison with the group of patients without diabetes mellitus. The group of patients with diabetes and unstable forms of coronary artery disease had significantly higher rates of spontaneous and adrenaline-induced platelet aggregation rate than the group of patients with stable coronary artery disease. A relationship was found between glycated hemoglobin levels above 7% and the rate of spontaneous and collagen-induced platelet aggregations.
Key words: coronary heart disease, diabetes mellitus, platelet aggregation.

An indisputable fact is the increase in the prevalence of diabetes mellitus (DM) to the scale of an epidemic [1]. The increase in life expectancy, as well as the prevalence of such modifiable risk factors (overweight and obesity, physical inactivity) are the determining reason for the increase in the number of patients with diabetes [2]. Nevertheless, there is ample evidence of the relationship between diabetes mellitus and cardiovascular diseases (CVD), and it became known that coronary heart disease (CHD) is the most common cause of death in patients with diabetes mellitus [3]. The results of large-scale studies (Framingham, MRFIT, Paris Prospective Study) led to the conclusion about the independent role of diabetes as a risk factor for cardiovascular diseases [4].

The genesis of chronic complications of diabetes is considered from the standpoint of glucose toxicity, since long-term hyperglycemia is an initiating factor in various biochemical and structural changes in cells and tissues in patients with diabetes. A prolonged hyperglycemia in diabetes leads to changes in the hemostatic system. The content of glycated hemoglobin in diabetes correlates with the content of fibrinopeptide A, antithrombin III, factor VII, fibrinogen [5].

In this regard, it was of interest to us to study the aggregation properties of blood in patients with diabetes and multivessel coronary lesions in relation to the duration of the disease, the level of glycemia and forms of CHD.

Material and research methods. 122 patients with ischemic heart disease (CHD) and type 2 diabetes, 67 men, 55 women (mean age 61.83 ± 19.5 years), were included in the study. Inclusion criteria for the study: the presence of CHD and type 2 diabetes mellitus in patients; angina pectoris and / or objective signs of myocardial ischemia; the presence of hemodynamically significant (> 50% in diameter) stenosis of the main epicardial coronary arteries; the primary nature of the narrowing of the native coronary arteries.

Exclusion criteria from the study: acute diabetic decompensation (diabetic ketoacidosis, hyperosmolar hyperglycemic state, diabetic lactic acidosis); terminal stages of diabetic micro- and macroangiopathies; severe impairment of kidney and liver function; acute disorders of cerebral circulation less than 6 months; decompensation of chronic heart failure; dysfunction of the thyroid gland in the stage of decompensation; oncological diseases; connective tissue diseases; other somatic diseases in the stage of decompensation, with an unfavorable immediate

prognosis; acute respiratory diseases and / or diseases of an infectious nature, transferred less than 3 months ago; over 75 years old; refusal to participate in the study; the perceived difficulties of subsequent prospective follow-up.

The average experience in diabetes mellitus was 8.3 ± 5.7 years. At the same time, 10 (8.2%) patients with diabetes were first diagnosed with diabetes during the first hospitalization, the duration of diabetes was less than 10 years in 24 (19.7%) patients, the anamnesis of diabetes was more than 10 years in 78 (63.4%) patients. We selected a group of patients without diabetes, but with comparable clinical characteristics, to obtain data on the features of antiplatelet therapy (APT).

Light aggregation was carried out on a two-channel laser analyzer "ALAT-2" by "BIOLA" (Russia). A platelet aggregation is determined by the traditional turbodimetric method in this device, by assessing the average size of the aggregates in real time, which are recorded in the form of oscillations. The method is based on platelet aggregation in platelet-rich plasma. Spontaneous aggregation without inducer injection and peak aggregation at 5 μM adenosine diphosphate (ADP) are taken into account. The blood for the study was taken from the cubital vein into a plastic test tube containing a 3.2-3.8% solution of trisodium citrate (sodium citrate) in a ratio (9:1) volumes of blood and sodium citrate. The platelet area under the aggregation curve, the degree and rate of platelet aggregation were assessed on the obtained aggregatograms.

Research results. As shown by a comparative analysis, the groups significantly differed in the severity of APT. Thus, the degree and rate of platelet aggregation upon induction of 0.1 μmol ADP were, respectively, 13.3 ± 8.5 rel. units and 26.2 ± 11%/min in the group of patients with diabetes, while in the group without diabetes the same indicators amounted to 7.2 ± 6.7 rel. units and 14.6 ± 12.9%/min, respectively (p=0.0008 and p=0.0005). A similar dynamics was observed with respect to the induction of 1.0 μM ADP. Thus, the indicator of the degree of aggregation was 20.2 ± 11.9 rel. units in the group of patients with diabetes, whereas in the group of patients without diabetes, the degree of aggregation was 10 ± 8.6 rel. units (p=0.0001), and the aggregation rate was 36.6 ± 13.4%/min and 22.1 ± 15.8%/min in the groups of patients with/without diabetes, respectively (p=0.0004). The increased aggregation activity was demonstrated by a group of patients with diabetes mellitus upon induction of platelet aggregation with 5.0 μM ADP. Thus, the degree of platelet aggregation in patients with diabetes was 31.5 ± 13.1 rel. units, while in the group of patients without diabetes it was significantly lower and amounted to 21.7 ± 13.2 rel. units (p = 0.003). The difference in the rate of 5.0 ADP-induced aggregation was also significant, as it was 45.8 ± 12.8%/min and 38.8 ± 15.9%/min in the group of patients with / without diabetes, respectively.

Table 1. Features of platelet aggregation activity in patients with CHD with / without diabetes

Indicators	DB	p	without DB
degree of platelet aggregation, %			
Spontaneous platelet aggregation, rel. units	1,3 ± 0,3	0,44	1,4 ± 0,5
Spontaneous platelet aggregation	3,7 ± 2,2	0,64	3,4 ± 2,4
0.1 μM ADP	13,3 ± 8,5	0,0008	7,2 ± 6,7
1.0 μM ADP	20,2 ± 11,9	0,0001	10 ± 8,6
5.0 μM ADP	31,5 ± 13,1	0,003	21,7 ± 13,2
0.2 mg / ml collagen	45,8 ± 21,4	0,41	41,3 ± 16,6
11 μM arachidonic acid	3,9 ± 3	0,53	2,2 ± 1,4
110 mmol adrenalin	44,8 ± 24,2	0,22	34,1 ± 19,6
von Willebrand factor	96,3 ± 28,6	0,004	65,8 ± 20,1
platelet aggregation rate,%/min:			
Spontaneous platelet aggregation	3,1 ± 1,6	0,95	3,1 ± 1,8
0.1 μM ADP	26,2 ± 11	0,0005	14,6 ± 12,9
1.0 μM ADP	36,6 ± 13,4	0,0004	22,1 ± 15,8
5.0 μM ADP	45,8 ± 12,8	0,07	38,8 ± 15,9
0.2 mg / ml collagen	23,1 ± 18	0,34	19,8 ± 14,9
11 μM arachidonic acid	3,7 ± 3,1	0,42	3,1 ± 2,7
110 mmol adrenalin	29 ± 14,1	0,53	19 ± 9,8

Analysis of collagen-induced platelet aggregation also revealed a similar trend, despite the absence of significant differences. Thus, the degree and rate of collagen-induced AT was 45.8 ± 21.4 rel. units and 23.1 ± 18%/min, respectively, in the group of patients with diabetes, whereas in the group of patients without diabetes, the same indicators were 41.3 ± 16.6 rel. units (p = 0.41) and 19.8 ± 8.9%/min, respectively (p = 0.34).

The rate and degree of platelet aggregation in the group of patients with diabetes were 3.9 ± 3 relative units and 3.7 ± 3.1% / min, respectively, with a test with arachidonic acid, and in the group of patients without diabetes, these indicators were 2.2 ± 1.4 relative units (p = 0.53) and 3.1 ± 2.7% / min (p = 0.42).

In the test with adrenaline, the differences were not significant, but nevertheless, a tendency to an increase in the rate and degree of platelet aggregation was observed in the group of patients with diabetes.

Analysis of the von Willebrand factor level showed its significant high level in the group of patients with diabetes, where it was 96.3 ± 28.6% versus 65.8 ± 20.1% in the group of patients without diabetes (p = 0.004).

We drew attention to the large spread of the standard deviation in the compared indicators and we decided to study APT within the group of patients with diabetes, depending on the forms of CHD.

Table 2. Features of platelet aggregation activity in patients with stable angina pectoris and unstable angina pectoris

Indicators	**Stable angina (n=20)**	p	Unstable angina (n=102)
degree of platelet aggregation, %			
Spontaneous platelet aggregation, rel. units	**1,32±0,3**	not reliable	1,34±0,3
Spontaneous platelet aggregation	**2,72±1,06**	not reliable	3.8±1,1
0.1 μM ADP	**12,78±8,9**	not reliable	14,6±8,2
1.0 μM ADP	**21,1±14,7**	not reliable	25,3±11,0
5.0 μM ADP	**30,6±11,76**	not reliable	35,8±10,9
0.2 mg / ml collagen	**39,8±15,17**	not reliable	41,8±14,9
11 μM arachidonic acid	**2,39±0,9**	0.02	5,1±0,8
110 mmol adrenalin	**30,14±8,5**	not reliable	39,83±7,9
von Willebrand factor	**76,9±3,69**	**0.007**	91,6±4,0
platelet aggregation rate,%/min:			
Spontaneous platelet aggregation	**2,09±0,82**	**0.03**	4,8±0,98
0.1 μM ADP	**25,89±6,2**	not reliable	30,9±5,8
1.0 μM ADP	**36,5±4,68**	not reliable	39,08±3,97
5.0 μM ADP	**45,3±3,5**	not reliable	47,13±2,9
0.2 mg / ml collagen	**19,22±5,9**	not reliable	19,6±4,8
11 μM arachidonic acid	**4,15±1,84**	not reliable	5,98±1,76
110 mmol adrenalin	**20,61±3,34**	0,04	27,9±3,1

Comparative analysis of platelet aggregation activity among patients with stable IHD and its unstable forms showed significant differences between the indicators of the degree of platelet aggregation induced by 11 μM arachidonic acid. Thus, in the group of patients with stable coronary artery disease, this indicator was 2.39 ± 0.9 rel. units, while in the group of patients with unstable forms of coronary artery disease, it was 5.1 ± 0.8 rel. units (p=0.02). The von Willebrand factor was also significantly higher in the group of patients with unstable angina than in patients with stable angina: 91.6 ± 4.0% versus 76.9 ± 3.69%, respectively (p = 0.007). The significant differences were also found between the rates of spontaneous platelet aggregation, which was significantly higher in the group with unstable angina, which amounted to 4.8 ± 0.98%/min versus 2.09 ± 0.82%/min in the group of patients with stable angina (p = 0.03). The rate of adrenaline-induced platelet aggregation was also significantly high in the group of patients with unstable CHD, which was 27.9 ± 3.1 %/min versus 20.61 ± 3.34 %/min in the group of patients with stable CHD (p = 0.04). Other indicators also demonstrated increased platelet aggregation in the group of patients with unstable CHD, but they did not reach statistical significance.

Table 3. Features of platelet aggregation activity in patients with CHD, depending on the level of glycated hemoglobin

Indicators	**less than 7% 7 (n=42)**	**P**	**7% and more (n=80)**
degree of platelet aggregation, %			
Spontaneous platelet aggregation, rel. units	**1.31±0.1**	not reliable	1.34±0.2
Spontaneous platelet aggregation	**2.29±1.1**	not reliable	3.9±1.09
0.1 μM ADP	**12.47±6.4**	not reliable	15.3±6.9
1.0 μM ADP	16.9±8.5	not reliable	27.0±9.1
5.0 μM ADP	**24.9±8.8**	not reliable	36.1±7.9
0.2 mg / ml collagen	**28.3±9.5**	not reliable	45.5±10.2
11 μM arachidonic acid	**2.68±0.8**	not reliable	4.3±0.9
110 mmol adrenalin	**28.4±7.5**	not reliable	36.9±8.0
von Willebrand factor	**74.8±4.46**	not reliable	89.9±6.2
platelet aggregation rate,%/min:			
Spontaneous platelet aggregation	**2.4±0.9**	**0.040035**	4.9±0.8
0.1 μM ADP	**25.02±4.48**	not reliable	31.3±5.1
1.0 μM ADP	**34.7±5.0**	not reliable	39.98±4.01
5.0 μM ADP	**43.1±4.2**	not reliable	48.3±3.98
0.2 mg / ml collagen	**15.4±2.85**	**0.011309**	24.3±1.96
11 μM arachidonic acid	**3.88±1.1**	not reliable	4.96±1.2
110 mmol adrenalin	**18.9±2.4**	not reliable	26.4±2.8

The group of patients with diabetes was divided into 2 subgroups depending on the level of glycated hemoglobin for the study of antiplatelet therapy: with an indicator of glycated hemoglobin less than 7% (42 patients) and with an indicator of glycated hemoglobin 7% or more (80 patients). Comparative analysis of the studied parameters showed a significant difference between the indicators of platelet aggregation, more pronounced in the group of patients with a glycated hemoglobin indicator of 7% and higher, but two parameters reached significant differences. Thus, the rate of spontaneous platelet aggregation was 4.9 ± 0.8% min in the group of patients with glycated hemoglobin of 7% and higher, while in the group of patients with a glycated hemoglobin level of less than 7% this indicator was 2.4 ± 0.9 (p = 0.04). Similarly, the rate of collagen-induced aggregation also showed a significant prevalence in the group with the level of glycated hemoglobin and was 24.3 ± 1.96% min versus 15.4 ± 2.85% min in the group with glycated hemoglobin below 7% (p = 0.01). In addition, a correlation was found between spontaneous platelet aggregation and glycated hemoglobin (r = 0.37 p = 0.014).

Table 4. Features of platelet aggregation activity in patients with CHD depending on the duration of diabetes

Indicators	**less than 10 years (n=44)**	**p**	**more than 10 years (n=78)**
degree of platelet aggregation, %			
Spontaneous platelet aggregation, rel. units	**1.30±0.1**	not reliable	1.34±0.2
Spontaneous platelet aggregation	**2.93±0.86**	not reliable	3.8±1.1
0.1 μM ADP	**11.64±3.2**	not reliable	17.3±2.98
1.0 μM ADP	14.39±5.1	not reliable	26.95±4.7
5.0 μM ADP	**23.1±4.4**	not reliable	34.8±5.3
0.2 mg / ml collagen	**25.98±3.9**	**0.003**	43.7±4.5
11 μM arachidonic acid	**2.15±0.4**	**0.002**	4.6±0.7
110 mmol adrenalin	**26.9±4.48**	not reliable	37.1±5.96
von Willebrand factor	**75.8±3.9**	**0.03**	88.0±4.3
platelet aggregation rate,%/min:			
Spontaneous platelet aggregation	**2.28±0.3**	**0.002**	4.1±0.5
0.1 μM ADP	**23.74±3.9**	not reliable	31.0±4.2
1.0 μM ADP	**34.1±5.6**	not reliable	39.5±4.3
5.0 μM ADP	**40.2±3.96**	not reliable	46.6±5.74
0.2 mg / ml collagen	**15.96±3.3**	not reliable	24.2±2.98
11 μM arachidonic acid	**3.5±0.98**	not reliable	4.1±1.5
110 mmol adrenalin	**18.4±2.1**	**0.04**	25.8±3.0

Analysis of antiplatelet therapy in patients with diabetes, depending on the length of the disease, also revealed significant differences between the compared groups. Thus, the degree of collagen-induced platelet aggregation was 43.7 ± 4.5 rel. units in the group of patients with DM lasting more than 10 years versus 25.98 ± 3.9 rel. units in the group of patients with diabetes less than 10 years old (p = 0.003). The degree of platelet aggregation induced by arachidonic acid was 4.6 ± 0.7 relative units in the group of patients with diabetes with a duration of more than 10 years and 2.15 ± 0.4 relative units in the group of patients with diabetes of less than 10 years (p = 0.002). The rate of spontaneous aggregation was 4.1 ± 0.5 in the group of patients with DM for more than 10 years versus 2.28 ± 0.3 in the group of patients with DM less than 10 years (p = 0.002). The rate of adrenaline-induced platelet aggregation was significantly higher in the group of patients with long-term diabetes mellitus - 25.8 ± 3.0%/ min versus 18.4 ± 2.1%/ min in the group of patients with diabetes mellitus duration less than 10 years (p = 0.04). Comparative analysis of the von Willebrand factor index also revealed significantly high values in the group of patients with long-term diabetes mellitus - 88.0 ± 4.3 versus 75.8 ± 3.9 in the group of patients with diabetes mellitus duration less than 10 years (p = 0.03).

Discussion. Cardiovascular diseases (CVD) are the leading cause of death in patients with diabetes mellitus (DM), accounting for 65-80% of deaths in these patients [6]. Thus, it has been shown that atherosclerosis develops more rapidly and aggressively in diabetes mellitus and more often leads to thrombotic events due to endothelial dysfunction and hypercoagulability [7]. In this regard, it was of interest to us to study the aggregation properties of blood in patients with diabetes and multivessel coronary lesions in relation to the duration of the disease, the level of glycemia and forms of CHD. We have selected patients with type 2 diabetes, suffering from ischemic heart disease, to solve this problem. The data of patients with type 2 diabetes were compared with the results of a comparable group of patients without diabetes to assess the aggregation activity of platelets. Significantly high differences were obtained in the indicators of ADP-induced platelet aggregation in patients with type 2 diabetes, which coincides with the data of Haffner S.M. et all. [8]. Comparative analysis of platelet aggregation activity in relation to the type of ischemic heart disease showed a significant increase in spontaneous aggregation and von Willebrand factor in patients with unstable forms of ischemic heart disease. Similar results were obtained by other authors [9]. Our data on the analysis of APT in patients with glycated hemoglobin coincide with the data of other researchers, where a significant excess of collagen-induced platelet aggregation was found [10].

Conclusion. Thus, the study of the features of antiplatelet therapy in patients with diabetes demonstrated a significantly pronounced ADP-induced rate and degree of platelet aggregation compared with the group of patients without diabetes.

The group of patients with diabetes and unstable CHD had significantly higher rates of spontaneous and adrenaline-induced platelet aggregation rate than the group of patients with stable CHD.

A relationship was found between the level of glycated hemoglobin above 7% and the rate of spontaneous and collagen-induced platelet aggregation.

The patients with long-term diabetes mellitus demonstrated significantly high levels of collagen-induced and arachidonic acid-induced platelet aggregation compared with the group of patients with diabetes mellitus duration less than 10 years. The rate of spontaneous and adrenaline-induced platelet aggregation was also significantly higher in the group of patients with a long history of diabetes mellitus.

References.

1.ESC Guidelines on diabetes, pre-diabetes and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD) // Eur Heart J. - 2013. - Vol. 34. №39. - P.3035-3087

2.IDF Diabetes Atlas.6-th edition. 2013. Available from: http://www.idf.org/ diabetesatlas., Lee P., Swarbrick M.M., Ho K.K.Y. Brown Adipose Tissue in Adult Humans: A Metabolic Renaissance // Endocrine Rewiews.- 2013. - Vol. 34. №3. - P.413-438.

3.Kalyagin A.N. Chronic heart failure: modern understanding of the problem. Features of patients with diabetes mellitus (the message 17) // Sibirskij Medicinskij Zurnal (Irkutsk). - 2008. -Vol. 80. №5. - P.93-99.

4.Wilson P.W., Anderson K.M., Kannel W.B. Epidemiology of Diabetes Mellitus in the Eldery: the Framingham Offspring Study.// Am. J. Med. - 1986. - Vol. 80 (5A). - P.3-9

5.С.А. Павлищук, А.В. Ромаш Сравнительная эффективность антиагрегантной терапии нарушений тромбоцитарного гемостаза при сахарном диабете второго типа. Кубанский научный медицинский вестник, 2015 стр 97-101

6.В.И.Новиков, К.Ю. Новиков. Антиагреганты при сахарном диабете. Consilium medicum. 2018.-N 4.-С.16-23.

7.В.И. Волков, С.А. Серик. Сахарный диабет и коронарный атеросклероз. Атеросклероз. 2011 т.7 номер 2 стр 5-22

8.Haffner S.M., Lehto S., Ronnema T. et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction// N. Engl. J. Med. 1998. Vol. 339. P. 229-234

9.В.В. Никонов, д.м.н., профессор, Е.И. Киношенко. Тромбоцитарный гемостаз и антитромбоцитарная терапия при остром коронарном синдроме. Новости медицины и фармации 2011. 374. Стр 9-14

10. О.А.Трубачева, И.В.Петрова. Изучение механизма коллаген-индуцированной агрегации тромбоцитов у пациентов с нарушением толерантности к углеводам или сахарным диабетом 2-го типа в сочетании с артериальной гипертензией. Сибирский журнал клинической и экспериментальной медицины. 2019. Том 34 номер 4.