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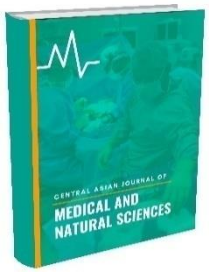

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Features of the Aggregate State of Blood in Patients with Ischemic Heart Disease Combined with Type 2 Diabetes Mellitus

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Abstract: The article presents an overview of a study on the aggregation state of blood in patients with coronary heart disease combined with type 2 diabetes mellitus. The presence of diabetes is associated with an increased risk of all forms of coronary heart disease, including angina pectoris, non-painful myocardial ischemia, myocardial infarction, as well as sudden cardiac death. As an ischemic heart disease, diabetes mellitus is also characterized by various disorders of coagulation, fibrinolysis, anticoagulant system, platelet function. These factors make a significant contribution to the appearance and progression of atherosclerosis and cardiovascular diseases in patients with type 2 diabetes mellitus. Coronary heart disease in diabetic patients, in comparison with patients without it, develops at an earlier age and is characterized by a more severe lesion of the coronary arteries with involvement of the distal bed. Diabetic disorders have been shown to trigger the natural mechanisms of platelet activation and reduce the levels of endogenous inhibitors of platelet activity.

Key words: coronary heart disease, diabetes mellitus, platelet aggregation, erythrocyte-platelet aggregates.

In the last decade, in the structure of morbidity and mortality of the population, cardiovascular diseases (CVD) occupy one of the first places both in Uzbekistan and around the world. The analysis shows that the mortality rate from CVD in 2021 was 61.7%, while the number of patients aged 18-74 years in men was 2 times higher than in women. According to statistics, in 2022, the mortality rate from CVD fell from 61.7% to 56.2% compared to 2021 [1, 5]. According to forecasts, by 2030, the cause of death is about 23.6 million. a person may develop from CVD, but the individual prognosis may change in a positive or negative direction depending on the diagnostic therapeutic and preventive measures carried out [1, 2, 4].

Cardiovascular diseases, especially coronary heart disease (CHD), are the main cause of death in diabetic patients [2]. Its relative risk is increased in men, depending on age, by 1.5—2.5 times, in women by 1.7—4 times.

CHD in diabetic patients, in comparison with patients without it, develops at an earlier age and is characterized by more severe damage to the coronary arteries with involvement of the distal bed. The presence of diabetes is associated with an increased risk of all forms of coronary heart disease, including angina, without painful myocardial ischemia, myocardial infarction, as well as sudden cardiac death. Recent years have been characterized by a steady increase in the number of patients with type 2 diabetes mellitus (DM). According to the forecasts of experts of the International Diabetes Association (IDF), by 2035 the number of DM patients in the world will reach 592 million people, almost every tenth inhabitant of the planet [7]. Such a disappointing prognosis makes it necessary for a timely and active intervention of a doctor in the treatment of this disease to reduce the risk of development and progression of micro- and macrovascular complications. Many studies conducted in various countries have demonstrated that diabetes is such a powerful risk factor for the development of cardiac pathology that it can be equated with the equivalents of coronary heart disease. Published population data from Finland (S.Haffner et al.) showed that mortality from acute myocardial infarction is the same in patients with DM without myocardial infarction and in people without DM with repeated myocardial infarction. The results of another OASIS study also proved that the risk of death due to any cardiovascular causes is exactly the same in patients with DM without a previous history of coronary artery disease and in patients without DM with a history of indications of cardiovascular diseases (K. Malmberg et al.). These data allowed the American Heart Association to classify diabetes as a cardiovascular disease. The reasons for such a high morbidity and mortality of DM patients from cardiovascular disasters is that in addition to risk factors common to the entire population, DM patients have specific factors - hyperglycemia, hyperinsulinemia, insulin resistance, disorders in the hemostasis system.

It is known that the most common cause of early disability and death of patients with diabetes mellitus (DM) in all countries of the world are its vascular complications, requiring extremely expensive treatment [14,15,16]. At the same time, early diagnosis and effective therapy of this formidable disease can delay or prevent the development of complications. At the same time, the issue of the causes of diabetic complications has not yet been finally resolved. It has been established that in diabetes, hemocoagulation and rheological disorders are observed, accompanied by endothelial dysfunction [16,17,18,19]. It is known that type 2 diabetes (DM2) occurs at an older age [14, 15], which should inevitably affect the state of the hemostasis system.

Ischemic heart disease (CHD) develops as a result of atherosclerosis of the coronary arteries, followed by their thrombosis and vessel occlusion. In the pathogenesis of thrombus formation, the leading role is played by changes in the functional activity of platelets, which are characterized by adhesion to collagen in areas uncovered by a layer of endothelium. External signs of platelet activation are a change in shape, an increase in the secretion of biologically active substances from granules, increased aggregation (AT). The direct activators of triggering these processes can be an increase in the shear rate, thrombin, adenosine diphosphate (ADP), collagen, biogenic amines, which also cause the release of the most powerful activator of aggregation of thromboxane A2 (THA2) [20]. As CHD, diabetes mellitus is also characterized by various disorders of coagulation, fibrinolysis, anticoagulant system, platelet function. These factors make a significant contribution to the appearance and progression of atherosclerosis and cardiovascular diseases in patients with DM2. In the work of C. Khawahd et al. it has been shown that the less satisfactory the indicators of carbohydrate metabolism, the more pronounced the disorders in the hemostasis system. Patients with diabetes mellitus are characterized by an atherothrombotic condition caused by multiple disorders in the hemostasis system.

Hemostatic disorders in patients with diabetes mellitus are usually complex and include activation of the natural mechanisms of the coagulation system, suppression of fibrinolytic activity, as well as various disorders of platelet function. In platelets, elevated glucose levels lead to the activation of

protein kinase C, a decrease in NO synthesis and an increase in oxygen synthesis. The platelet membrane contains glycoproteins (GP) – receptors of adhesive proteins. In diabetic patients, there is an increased expression of glycoprotein Ib (GP Ib) on the platelet surface, which determines platelet binding to the Willebrand factor. The interaction of GP Ib and Willebrand factor induces an intracellular signal that leads to the activation of the GP IIb/IIIa complex, which allows the binding of fixed and dissolved Willebrand factor and plasma fibrinogen. In this case, a contractile cytoskeleton is formed and the contents of platelet granules are isolated, which induces vasoconstriction and platelet aggregation [3,28]. These disorders may be caused by a decrease in the endothelial synthesis of antiplatelet agents – nitric oxide and prostacyclin and an increase in the formation of platelet activators, such as thrombin and Willebrand factor. Thus, diabetic disorders trigger the natural mechanisms of platelet activation and reduce the levels of endogenous inhibitors of platelet activity.

One of the factors contributing to platelet activation can be red blood cells. In addition to transport, plastic, buffering and a number of others, hemostatic is an important function of erythrocytes [14]. The change in the properties of erythrocytes accompanying many pathological processes in the body leads to an increase in their aggregation (AE), a decrease in deformability and resistance (RE), which can contribute to thrombosis. On the one hand, this effect may be associated with the release of ADP from erythrocytes, which stimulates AT [24], and on the other hand, with the activation of adhesion molecules on erythrocytes [22] or exposure to phosphatidylserine [36]. Procoagulant properties of erythrocytes are characteristic of their hemolysate [9].

The following processes can serve as possible reasons for an increase in blood clotting: when red blood cells are destroyed, in addition to the thromboplastin factor, ADP is released, which not only causes AT, but also facilitates the activation of Hageman factor, contributing to the initiation of the internal coagulation pathway;

- the appearance of lysed erythrocytes in the circulating blood is accompanied by the release of endogenous amines;
- intravascular hemolysis is accompanied by pronounced activation of the kinin system;
- the appearance of destroyed erythrocytes in the vascular bed contributes to the development of secondary hypercoagulation due to the reflex release of tissue (vascular) thromboplastin into the blood. In patients with impaired erythrocytes and thrombosis in the blood, the formation of thrombin increases. It is found in the hemolysate of erythrocytes and is associated with the separation of microvesicles from these cells [27]. The formation of microvesicles with procoagulant activity is regulated by membrane phosphatidylserine [21]. The interaction of erythrocytes with platelets and the formation of erythrocyte-platelet aggregates (ETA) plays an essential role in the activation of the platelet link of hemostasis [8].

The mechanisms of ETA formation have not been definitively clarified to this day; perhaps their appearance in the blood is associated with endotoxinemia [11,13]. Erythrocytes can modulate platelet function through physical interactions between cells; such interactions are enhanced with increasing shear stress strength. Erythrocytes contain a large number of adhesion molecules on the membrane, which are necessary for their interaction with leukocytes, platelets and endothelium. Many of these molecules have a protein chain characteristic of representatives of the family of immunoglobulins performing the recognition function. The adhesion molecule ICAM-4 (intracellular adhesive molecule) expressed on the surface of erythrocytes can bind to a ligand on platelets, which is glycoprotein IIb/IIIa, which leads to interaction between these cells and the appearance of a heterocellular aggregate [26].

Native erythrocytes do not interact with other circulating blood cells and the vascular wall under normal conditions, which indicates the inaccessibility of their adhesion molecules to their ligand. But

in pathological conditions, with malaria [30], sickle cell anemia [25] and diabetes (DM) [32], inert red blood cells acquire the ability to interact with other blood cells. This formation leads to further activation of platelets and an increase in the proaggregant activity of the extracellular medium as a result of the release of biologically active substances from these cells, such as THA2 and ADP. At the same time, substances secreted by platelets trigger the procoagulant activity of erythrocytes [34]. An important role in stimulating the functional activity of platelets by erythrocytes is played by the activation of platelet cyclooxygenase (COX), which catalyzes the formation of prostaglandin H2 from arachidonic acid [31]. The physical interaction of erythrocytes and platelets activates phospholipase A2 and the release of arachidonic acid, which in turn causes the formation of THA2 and increases serotonin release from platelets by 2 times and further involves all new platelets in the interaction. Circulating ETA can be observed in patients 1 day after coronary bypass surgery [35]. Erythrocytes can contribute to the deposition of platelets on the subendothelium, and this process is directly proportional to hematocrit [33]. Such an increase in platelet reactivity can contribute to atherothrombotic and proliferative processes in the vascular wall, which is important from a clinical point of view. In addition to the participation of erythrocytes in hemostasis processes, their role in the development of rheological disorders is generally recognized [14,23]. An increase in blood viscosity is associated with an increase in the number of red blood cells, the appearance of aggregates or a decrease in their deformability [29], as well as a change in their shape [6]. The ability of erythrocytes to aggregate is due to an increase in blood viscosity at low shear rates. In experimental thrombosis, a significant number of flattened erythrocytes with processes, teardrop-shaped, prone to increased destruction appear in the bloodstream [6]. Physiological AE is a reversible process.

In a healthy organism, disaggregation dominates aggregation. The imbalance of these forces determines the increase in the aggregation capacity of red blood cells. The ability of erythrocytes to form aggregates depends on hemodynamic, plasma, electrostatic, mechanical, membrane and other reasons. Risk factors for the development of atherothrombosis, such as hyperlipidemia, diabetes, hypertension, inflammation and hyperfibrinogenemia contribute to the strengthening of not only AT, but also AE, which disrupts blood rheology [4]. In patients with coronary heart disease, blood rheology disorders are most pronounced in acute myocardial infarction (AMI) and unstable angina; they are accompanied by an increase in AE and a decrease in their deformability [10,12]. In patients suffering from chronic lung diseases and coronary heart disease, an increase in hemolysis and a decrease in the life expectancy of red blood cells were also noted [7].

Thus, in the world literature there is a large number of works devoted to violations of the hemostasis system in ischemic heart disease in combination with diabetes mellitus. The available results mainly confirm the fact that in these conditions, pronounced disorders of all parts of the hemostasis system develop, which contributes to the development and progression of micro- and macrovascular complications.

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