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Assessment of Factors of Vascular Wall Damage in Depressed Patients After Myocardial Infarction

Mukhamadiyeva N. B.
Bukhara State Medical Institute; Department of Psychiatry, Narcology and Medical Psychology, email: muxamadiyeva.nigina@bsmi.uz

Annotation: The study of pathogenetic predictors of the development of anxiety–depressive disorders in myocardial infarction (MI) will make it possible to develop approaches to their correction, thereby reducing the frequency of complications in the post-infarction period. To assess the mental status of the subjects, subjective methods were used, including the Hospital Anxiety and Depression Scale (HADS), designed for somatic hospital patients and recommended for use in individuals during the post-infarction period. Markers of endothelial dysfunction in blood plasma were determined by enzyme-linked immunosorbent assay using appropriate test systems. Since fibrinogen is one of the key factors in the blood coagulation process, disturbances of which—with a tendency toward thrombotic changes—represent a central link in the pathogenesis of MI, the level of oxidized fibrinogen was studied alongside indicators of the functional state of endothelial cells. The identified signs of thrombotic and hypercoagulable abnormalities in the hemostasis system in MI patients with depressive disorders possess high diagnostic value.

Keywords: post-infarction depression, comorbidity, risk factors, pathogenetic predictors, oxidized fibrinogen, endothelial dysfunction.

Introduction

A wide range of diseases is accompanied by the development of affective disorders, including depression, resulting in changes in the patient's perception, emotional experience, and evaluation of events in daily life. This leads to disturbances in interpersonal relationships and a decline in quality of life. It is well known that depression is very often comorbid with various somatic diseases, and in such cases, conditions from two different domains—mental and somatic—mutually aggravate each other, sometimes resulting in severe consequences. This is especially true for cardiovascular diseases [1,2,3,4,5].

Depression comorbid with myocardial infarction significantly predisposes to a three- to fourfold increase in cardiovascular mortality and is closely correlated with the worsening of clinical symptoms of MI and a poorer prognosis of the disease. One of the key factors determining the course and prognosis of myocardial infarction is the development of anxiety–depressive disorders (ADD). Manifestations of a major depressive episode occur in 15–20% of patients with this diagnosis. In the post-infarction period, depression is detected in 16–45% of cases. American researchers have shown that increased mortality after myocardial infarction is associated even with minimal symptoms of depression.

Therefore, alongside the diagnostic procedures performed (instrumental and biochemical), it is necessary to pay close attention to psychological testing of patients with myocardial infarction (MI) in order to identify anxiety–depressive disorders [14,15, 16]. Although the number of studies devoted to depression in post-infarction patients is relatively small, there is evidence that without treatment, depression acquires a chronic course within the first year after MI [6,7,8,9]. Thus, the analysis of the literature shows that the development of depressive disorders is associated with the worsening of pathophysiological changes characteristic of coronary artery disease and MI in particular. However, the pathophysiological mechanisms underlying the relationship between depression and myocardial

infarction—and most importantly, the mechanisms of depression development in MI—remain insufficiently studied.

In view of the above, the search for pathogenetic predictors of the development of anxiety–depressive disorders in MI appears highly relevant. Identifying such predictors would allow the development of approaches to their correction, thereby reducing the incidence of complications during the post-infarction period, which served as the objective of our study. Based on this rationale, we aimed to examine the levels of oxidized fibrinogen and the parameters of endothelial cell functional status in patients who had experienced myocardial infarction with clinical manifestations of depressive syndrome (the main group), compared to patients who had suffered myocardial infarction without depressive symptoms (the control group) [10,11,12]. This biochemical panel was selected because fibrinogen is one of the key components of the blood coagulation process, and disturbances in this system represent one of the central links in the pathogenesis of myocardial infarction [15]. At present, the mechanisms underlying the interaction between changes in oxidized fibrinogen levels and the functional parameters of endothelial cells in MI patients with depressive disorders remain insufficiently investigated.

Materials and Methods

The clinical study was based on the examination of 58 patients with MI (mean age 59.2 ± 4.7 years) admitted for treatment to a cardiology hospital, as well as on data obtained during their rehabilitation period. According to the presence of anxiety–depressive symptoms, the patients were divided into two groups. The first (control) group consisted of 14 patients who had suffered MI without depressive disorders. The second group included 44 age-matched patients who had experienced myocardial infarction accompanied by symptoms of anxiety and depression, without comorbid cardiovascular pathology.

The diagnosis of myocardial infarction was based on clinical examination findings, ECG changes, laboratory parameters, and echocardiographic data. Biochemical assessments and evaluations of mental status were conducted on days 30, 90, 180, and 360 after MI. Upon admission, all patients received standard treatment, including therapy for concomitant diseases. To assess the mental status of the subjects, subjective methods were used—the Hospital Anxiety and Depression Scale (HADS), developed by A. Zigmond and R. Snaith (1983) [11] for somatic hospital patients and recommended for use in individuals during the post-infarction period.

Blood samples were collected during the first 72 hours after destabilization of the clinical condition due to MI, once, after obtaining informed consent from each patient. Markers of endothelial dysfunction in blood plasma were determined by enzyme-linked immunosorbent assay using appropriate test systems (“Diagnostica Stago” and “Bender MedSystems,” Austria). All analyses were performed using the COBAS-411 automated immunoassay analyzer.

The degree of oxidative modification was measured relative to a specific blood glycoprotein—fibrinogen. First, the fibrinogen concentration was determined: from 1 ml of nitrate (3.8% citrate) blood plasma, fibrin polymer was isolated by precipitation after adding 0.5 ml of a 20 mM $CaCl_2$ solution. The sample was then incubated in a water bath at 37°C for 10 minutes; the resulting clot was dried on a paper filter, weighed on torsion balances, and its mass converted to fibrinogen content.

Next, 0.5 ml of a 0.9% NaCl solution and the same volume of a 20% TCA solution were added to the clot for denaturation and additional protein precipitation. The oxidative modification of the clot was then determined. To 100 µl of blood serum, 0.9 ml of a 20% trichloroacetic acid (TCA) solution was added for protein precipitation and denaturation; then 1 ml of a 0.1 M 2,4-dinitrophenylhydrazine (2,4-DNPH) solution in 2 M HCl was added. The sample was incubated at room temperature for 1 hour, centrifuged at 3000 g for 20 minutes, and the precipitate was washed three times with 1 ml of an ethanol:ethyl acetate (1:1) mixture to remove excess 2,4-DNPH that had not reacted with carbonyl groups of oxidized proteins. The precipitate was dried and then dissolved in 2.5 ml of an 8 M urea solution with the addition of 15 µl of 2 M HCl. In the control sample, 1 ml of 2 M HCl was added

instead of 2,4-DNPH. The degree of oxidative protein modification was determined by measuring the optical density of the resulting dinitrophenylhydrazones using spectrophotometry at a wavelength of 363 nm. The results were expressed in optical density units per ml of plasma (oxidized fibrinogen, OD units/mg fibrinogen/ml plasma) (Ragino Yu.I. et al., 2007).

Statistical analysis of the obtained data was performed using the Statistica 9.0 software package. The significance of differences between mean values was assessed using Student's t-test. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion

Oxidative stress plays a significant role in the development of cardiovascular diseases and atherosclerosis. The onset of oxidative stress is associated with the activation of intracellular signaling pathways by reactive oxygen species and modified lipids and proteins. It has been shown that in atherosclerosis, oxidative stress leads to endothelial damage, promotes inflammatory processes, facilitates the migration of leukocytes and monocytes, contributes to the formation of foam cells, and stimulates the migration and proliferation of smooth muscle cells, resulting in plaque formation. Oxidized lipoproteins play an important role in these processes. However, proteins—particularly fibrinogen—can also undergo oxidative modification.

Fibrinogen is an independent risk factor for the development of atherosclerosis and cardiovascular complications. It is known that atherosclerotic plaque progression is accompanied by the accumulation of fibrinogen and fibrin within the plaque. It has also been demonstrated that fibrinogen induces vascular intima thickening, and its high plasma levels are associated with increased thrombogenesis, a higher risk of stroke and myocardial infarction, and a greater likelihood of complications after cardiac surgery. Importantly, fibrinogen is among the proteins most sensitive to oxidative stress.

Since MI is closely associated with lipid oxidation, as mentioned above, we hypothesized that oxidized fibrinogen—along with oxidized lipoproteins—may be present in blood plasma or within the vascular wall and contribute to pathological processes observed in MI. Oxidized fibrinogen may induce apoptosis in endothelial cells, which, according to published data, is one of the causes of thrombus formation during acute vascular syndromes (Aseichev A.V. et al., 2011). In this regard, at the next stage of the study, we investigated the effects of oxidized fibrinogen forms on endothelial cell apoptosis in patients who had experienced myocardial infarction with the development of depressive syndrome.

Since fibrinogen is one of the key factors in the blood coagulation process, disturbances of which—with a tendency toward thrombotic changes—constitute one of the central mechanisms in MI pathogenesis, we examined the level of oxidized fibrinogen alongside parameters of endothelial cell functional status. In the early period after MI, the level of oxidized fibrinogen was 1.7 times higher in the main group compared to the control, although the overall fibrinogen level remained within normal limits. In subsequent stages of the study, the oxidized fibrinogen level remained elevated and, on average, exceeded control values by 1.64 times (Table 1).

Table 1. Parameters of Oxidative Modifications of Fibrinogen and Endothelial Function in the Plasma of Examined Subjects**

Indicator	1 month		3 months		6 months		12 months	
	Control (n=30)	Main group (n=30)	Control (n=30)	Main group (n=30)	Control (n=30)	Main group (n=30)	Control (n=30)	Main group (n=30)
Oxidized fibrinogen, OD units/mg fibrinogen/ml plasma	10.6 ± 0.72	18.4 ± 1.13	10.2 ± 0.54	17.1 ± 0.93	9.8 ± 0.84	17.4 ± 1.15	9.6 ± 1.12	16.9 ± 1.17
Fibrinogen, g/L	3.1 ±	4.4 ±	3.0 ±	4.28 ±	2.9 ±	4.2 ±	2.9 ±	4.1 ±

	0.16	0.14	0.12	0.32	0.14	0.24	0.11	0.26
Endothelin-1, pmol/L	306.7 ± 37.2	484.5 ± 46.0**	272.3 ± 23.4	465.8	248.6 ± 17.8	443.1 ± 11.7	226.3 ± 27.8	415.6 ± 13.8
von Willebrand factor, IU/ml	1.1 ± 0.12	2.7 ± 0.24**	1.0 ± 0.18	2.3 ± 0.12	0.8 ± 0.14	2.2 ± 0.16	0.7 ± 0.16	1.8 ± 0.13

Notes: $p < 0.05$; **p** < 0.01 versus control.

Discussion

Disturbances in vascular–platelet hemostasis are closely associated not only with functionally altered fibrinogen but also with the condition and functional integrity of the vascular endothelium, which plays an essential role in the development of atherothrombotic complications. The identified relationship between oxidized fibrinogen, oxidative processes, and endothelial dysfunction determined the need to investigate the potential impact of oxidized fibrinogen on endothelial function.

It is known that the von Willebrand factor (vWF) is a hemostatic component that stabilizes the procoagulant protein factor VIII:C and enhances platelet adhesion to the subendothelium via glycoprotein Ib receptors, as well as platelet–platelet interaction through glycoprotein IIb/IIIa receptors. The latter represent a key interaction point for both vWF and fibrinogen.

Significant potentiation of platelet adhesion and aggregation has been demonstrated through activation of IIb/IIIa receptors at elevated vWF levels in the presence of oxidized fibrinogen. This allows the combined elevation of these factors in the bloodstream to be regarded as one of the central predictors of hypercoagulation.

Conclusion

In our study, an increase in plasma von Willebrand factor levels was observed in the early period after myocardial infarction (MI) with depressive symptoms, amounting to a 2.5-fold elevation compared with the control group. The plasma level of endothelin-1 was also significantly higher in the early post-MI period, exceeding control values by 1.6 times. Given that oxidative stress plays a key role in the development of endothelial dysfunction and destruction, a correlation analysis was performed to assess the relationship between oxidative modification of fibrinogen and endothelial function parameters.

A direct correlation was identified between oxidized fibrinogen levels and endothelin-1 ($r = 0.78$, $p < 0.01$), as well as between oxidized fibrinogen and von Willebrand factor ($r = 0.365$, $p < 0.01$). Linear regression analysis confirmed the association of oxidized fibrinogen with these markers of endothelial dysfunction.

Correlation analysis between the development of post-infarction depression and biochemical blood parameters at different follow-up time points demonstrated inverse correlations with fibrinogen levels ($r = –0.467$), oxidized fibrinogen ($r = –0.514$), endothelin-1 ($r = –0.373$), and von Willebrand factor ($r = –0.374$).

Based on the obtained results, it can be emphasized that in MI patients with depressive symptoms, in addition to elevated oxidative modifications of plasma lipids and proteins, a marked oxidative modification of fibrinogen is also present, which does not depend on the total fibrinogen concentration. Oxidized fibrinogen potentiates prothrombotic alterations within the vascular–platelet component of hemostasis, particularly by accelerating leukocyte–platelet aggregation. The identified signs of thrombotic and hypercoagulable disturbances in the hemostatic system—such as manifestations of endothelial dysfunction and elevated von Willebrand factor—are closely associated with oxidative fibrinogen modifications in MI patients who develop depressive symptoms. These findings have high diagnostic value.

- In myocardial infarction (MI) patients who develop depressive syndrome (DS), along with increased oxidative modifications of plasma lipids and proteins, a pronounced oxidative modification of fibrinogen is also observed, which does not depend on the fibrinogen

concentration. Oxidized fibrinogen potentiates prothrombogenic alterations within the vascular–platelet component of hemostasis, particularly by accelerating leukocyte–platelet aggregation. The identified signs of thrombotic and hypercoagulable disturbances in the hemostatic system in MI patients with depressive disorders—such as manifestations of endothelial dysfunction and elevated von Willebrand factor levels—are associated with oxidative modifications of plasma fibrinogen and have high diagnostic value.

- The study of platelet functional status, hemostasis parameters, and the level of endothelial-damaging factors (such as homocysteine) in patients who have experienced myocardial infarction with DS at different stages of follow-up indicates an intensification of apoptosis due to endogenous intoxication and oxidative stress.
- In the development of endothelial dysfunction in patients after myocardial infarction with depressive disorders (DD), endothelial-damaging factors play a decisive role. These factors contribute to enhanced plasma-coagulation and platelet thrombophilia in MI patients with depressive syndrome. The biochemical basis of endothelial dysfunction induced by endothelial-damaging factors lies in increased production of thrombo-regulatory substances, adhesion molecules, acceleration of apoptosis, and oxidative stress, ultimately leading to increased thrombophilia in this patient population.

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