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Assessment Of Factors Of Vascular Wall Damage In Depressive Disorders In Patients With Myocardial Infarction

Mukhamadieva N.B.
Bukhara State Medical Institute; Department Of Psychiatry, Narcology And Medical Psychology; Bukhara, Uzbekistan

ABSTRACT

The study of pathogenetic predictors of the development of anxiety-depressive disorders in myocardial infarction will make it possible to develop ways of their correction, thereby reducing the frequency of complications of the postinfarction period. Clinical studies were based on the examination of 58 patients with MI (mean age 59.2 ± 4.7 years) who were admitted to the cardiological hospital for treatment, and the observation data for them at the stage of rehabilitation. On the basis of the presence of anxiety-depressive symptoms, the patients were divided into 2 groups. The first control group consisted of 14 patients with MI without depressive disorders. The second group included 44 age-matched patients who underwent MI with symptoms of anxiety and depression without comorbid cardiovascular pathology. The diagnosis of myocardial infarction was based on the results of clinical examination, ECG changes, laboratory parameters, and echocardiographic data. In order to assess the mental status of the subjects, subjective methods were used: the hospital anxiety and depression scale (HADS) for patients in a somatic hospital and recommended for use in patients with post-infarction period. Markers of endothelial dysfunction in blood plasma were determined by enzyme immunoassay using appropriate test systems. Since fibrinogen is one of the key factors in the blood coagulation process, disorders of which with a tendency to thrombotic changes are one of the central links in the pathogenesis of MI, the level of oxidized fibrinogen with parameters of the functional state of endothelial cells was studied. In the early stages after myocardial infarction, the level of oxidized fibrinogen was 1.7 times higher in the study group compared to the control, although, in general, the level of fibrinogen in the study group was within normal values. In the subsequent periods of the study, the level of oxidized fibrinogen was in high values and, on average, exceeded the control values by 1.64 times. Since one of the key roles in the development of dysfunction and endothelial destruction is assigned to the factors of oxidative stress, a correlation analysis of the relationship between the oxidative modification of fibrinogen and the parameters of endothelial function was carried out. A direct correlation was shown between the level of oxidized fibrinogen and

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the level of Endothelin-1 ($r = 0.78$, $p < 0.01$), and a direct correlation with the level of von Willebrand factor ($r = 0.365$, $p < 0.01$). Linear regression analysis confirmed the associations of oxidized fibrinogen with the indicated parameters of endothelial dysfunction. Based on the results obtained, it can be emphasized that with MI, in patients with developed DS, along with increased oxidative changes in lipids and plasma proteins, there is also a significant oxidative modification of fibrinogen, which does not depend on the concentration of fibrinogen. Oxidized fibrinogen potentiates potentially prothrombogenic changes in the vascular-platelet link of hemostasis, in particular, the acceleration of leukocyte-platelet aggregation. The revealed signs of thrombotic and hypercoagulant hemostasis disorders in patients with MI with depressive disorders, such as signs of endothelial dysfunction, elevated von Willebrand factor levels, are associated with oxidative changes in plasma fibrinogen in patients with MI with the development of DS, have a high diagnostic value.

KEYWORDS

Postinfarction depression, comorbidity, risk factors, pathogenetic predictors, oxidized fibrinogen, endothelial dysfunction.

INTRODUCTION

A number of diseases are accompanied by the development of affective disorders, including depression, as a result of which the character of the patient's sensations, his perception and assessment of the events of the surrounding reality change, which leads to disturbances in interpersonal relationships and a deterioration in the quality of life. It is known that depression is very often comorbid with other, somatic, diseases, and in such cases, diseases of two different spheres - mental and somatic - aggravate each other, sometimes leading to serious consequences. This is especially true for diseases of the cardiovascular system [1,2,3,4,5]. Depression comorbid to myocardial infarction predetermines a three to fourfold increase in cardiovascular mortality, and also closely correlates with the worsening of the clinical symptoms of myocardial infarction and the worsening of the prognosis of this pathology. One of the factors that determine the course and prognosis of myocardial infarction (MI) is the development of anxiety-depressive disorders (TDR). The manifestations of a major depressive episode occur in 15-20% of patients with this nosological form. In patients in the postinfarction period, depression is found in 16-45% of cases. American scientists have shown that an increase in mortality after myocardial infarction is associated with even minimal symptoms of depression. Therefore, along with diagnostic measures (instrumental and biochemical) in patients with MI, attention should be paid to psychological testing of patients to identify anxiety-depressive

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disorders [14,17,18,26]. Although the number of studies on depression in postinfarction patients is relatively small, there is some evidence that without treatment it becomes chronic within a year after myocardial infarction [6,7,8,9]. Thus, an analysis of the literature data showed that the development of depressive disorder is associated with an aggravation of the pathophysiological changes characteristic of coronary heart disease and MI, in particular. However, the pathophysiological mechanisms of the relationship between depression and myocardial infarction, and most importantly, the mechanisms of the development of depression in myocardial infarction, have not been fully studied.

In connection with the above, it seems relevant to search for pathogenetic predictors of the development of anxiety-depressive disorders in myocardial infarction, which will make it possible to develop ways to correct them, thereby reducing the incidence of post-infarction complications, which was the purpose of our study. Based on the foregoing, it was of interest to us to study the level of oxidized fibrinogen with the parameters of the functional state of endotheliocytes in patients with myocardial infarction with clinical manifestations of depressive syndrome, which constituted the main group and patients who had suffered myocardial infarction without clinical manifestations of depressive syndrome (control group) [10,11,12]. A set of biochemical studies was chosen because fibrinogen is one of the main factors in the blood coagulation process, the violation of which is one of the key links in the pathogenesis of myocardial infarction [19]. Currently, the mechanisms of interaction of changes in the level of oxidized fibrinogen with the parameters of the functional state of endothelial cells in patients with MI with depressive disorders have not been sufficiently studied.

MATERIALS AND METHODS

Clinical studies were based on the examination of 58 patients with MI (mean age 59.2 ± 4.7 years) who were admitted to the cardiological hospital for treatment, and the observation data for them at the stage of rehabilitation. On the basis of the presence of anxiety-depressive symptoms, the patients were divided into 2 groups. The first control group consisted of 14 patients with MI without depressive disorders. The second group included 44 age-matched patients who underwent MI with symptoms of anxiety and depression without comorbid cardiovascular pathology. The diagnosis of myocardial infarction was based on the results of clinical examination, ECG changes, laboratory parameters, and echocardiographic data. Biochemical studies and assessment of mental status were carried out in patients at 30,90,180 and 360 days after MI. All patients on admission to the hospital received standard treatment, including therapy for comorbidities. In order 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 patients of a somatic hospital and recommended for use in patients with postinfarction period [14, 23, 24, 25]. Blood samples were taken from patients in the first 72 hours after the destabilization of the clinical state of myocardial infarction once after obtaining the informed consent of each patient. Markers of endothelial dysfunction in blood plasma were determined by enzyme immunoassay using appropriate test systems (DiagnosticaStago and BenderMedSystems, Austria). The studies were carried out on an

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automatic enzyme immunoassay analyzer COBAS-411. The degree of oxidative modification was measured relative to a separate blood glycoprotein, fibrinogen. First, the concentration of fibrinogen is determined: from 1 ml of nitrate (3.8% citrate) blood plasma, fibrin-polymer is isolated by precipitation by adding 0.5 ml of 20 mM CaCl2 solution, then the sample is incubated in a water bath at 37 ° C for 10 minutes, a clot formed dried on a paper filter, weighed on a torsion balance and recalculated its weight for fibrinogen. Then 0.5 ml of 0.9% NaCl solution and the same volume of 20% TCA solution are added to the clot for denaturation and additional protein precipitation. Next, the oxidative modification of the clot is determined. 0.9 ml of 20% trichloroacetic acid (TCA) solution is added to 100 µl of blood serum for precipitation and denaturation of proteins, 1 ml of 0.1 M solution of 2,4-dinitrophenylhydrazine (2,4-DNPH) in 2 M HCl solution is added, the sample is incubated at room temperature for 1 h, centrifuged at 3000 g for 20 minutes, the precipitate is washed 3 times with 1 ml of ethanol: ethyl acetate (1: 1) solution to extract excess 2,4-DNPH that has not reacted with the carbonyl groups of oxidized proteins, precipitate dried and then dissolved in 2.5 ml of 8 M urea solution with the addition of 15 µl of 2 M HCl solution. Instead of 2,4-DNPH, 1 ml of 2 M HCl solution is added to the control sample. The degree of oxidative modification of proteins is determined by measuring the optical density of the formed dinitrophenylhydrazones
spectrophotometrically at a wavelength of 363 nm. The results are expressed in units of optical density ml of plasma (oxidized fibrinogen, units / mg of fibrinogen / ml of plasma) (Ragino Yu.I. et al, 2007). Statistical processing of the obtained data was carried out using the Statistica 6.0 for Windows application software package. The significance of differences between the mean values was assessed by Student's t. Differences were considered statistically significant at $p < 0.05$.

RESEARCH RESULTS AND DISCUSSION

Oxidative stress is involved in the development of cardiovascular disease and atherosclerosis. The development 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 oxidative stress in atherosclerosis leads to endothelial damage, the development of inflammatory processes, promotes the migration of leukocytes and monocytes, the formation of foam cells, migration and proliferation of smooth muscle cells, and the formation of plaques. Oxidized lipoproteins play an important role in these processes. However, proteins, in particular fibrinogen, can also undergo oxidative modification. Fibrinogen is an independent risk factor for the development of atherosclerosis and complications of cardiovascular diseases. It is known that the progression of atherosclerotic plaque is accompanied by the accumulation of fibrinogen and fibrin in it. It was also shown that fibrinogen causes a thickening of the intima of the vessels, and its high content in plasma is associated with an increase in thrombus formation, the risk of stroke and heart attack, the risk of complications after cardiac surgery. It is important to note that fibrinogen is the protein most sensitive to the effects of oxidative stress. Since MI is closely associated with lipid oxidation, as mentioned above, we suggested that oxidized fibrinogen, along with oxidized lipoproteins, may appear in the blood plasma or in the wall of blood vessels and contribute to the pathological processes

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observed in MI. Oxidized fibrinogen can cause apoptosis of endothelial cells, which, according to the literature, is one of the causes of thrombus formation in the case of acute vascular syndromes (Aseichev A.V. et al., 2011). In this regard, at the next stage of research, we studied the effect of oxidized forms of fibrinogen on apoptosis of endothelial cells of blood vessels in patients who underwent myocardial infarction with the development of DS.

Since fibrinogen is one of the key factors in the blood coagulation process, disorders of which with a tendency to thrombotic changes are one of the central links in the pathogenesis of MI, the level of oxidized fibrinogen with parameters of the functional state of endothelial cells was studied. In the early stages after myocardial infarction, the level of oxidized fibrinogen was 1.7 times higher in the study group compared to the control, although, in general, the level of fibrinogen in the study group was within normal values. In the subsequent periods of the study, the level of oxidized fibrinogen was in high values and, on average, exceeded the control values by 1.64 times (table 1).

Table 1

Parameters of oxidative changes in fibrinogen and endothelial function in plasma of examined individuals

Index	1 month		3 month		6 month		12 month	
	Control gr. N=30	main group N=30	Control gr. N=30	main group N=30	Control gr. N=30	main group N=30	Control gr. N=30	main group N=30
Oxidized fibrinogen, U / 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± 0,16	4,4± 0,14	3,0± 0,12	4,28+ 0,32	2,9± 0,14	4,2± 0,2 4	2,9± 0,11	4,1± 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

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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

Violations of vascular-platelet hemostasis are closely associated not only with functionally altered fibrinogen, but also with the state of the vascular endothelium, as well as its functions, which is important in the development of atherothrombotic complications. Revealing the relationship of oxidized fibrinogen with oxidation processes and disorders of the endothelial system determined the need to study the possible effect of oxidized fibrinogen on endothelial function. It is known that von Willebrand factor is a hemostasis factor that stabilizes the procoagulant protein factor VIII: C and potentiates platelet adhesion to the subendothelium via glycoprotein receptors Ib, as well as platelet interaction via glycoprotein receptors IIb / IIIa. The latter are the point of interaction between von Willebrand factor and fibrinogen. A significant potentiation of platelet adhesion and aggregation through the activation of IIb / IIIa receptors with an increased level of von Willebrand factor in the presence of oxidized fibrinogen has been shown, which allows considering a combined increase in blood concentrations of these factors as one of the key predictors of hypercoagulation.

In the study of von Willebrand factor in plasma, we noted an increase in this indicator in the early stages after myocardial infarction with DS by 2.5 times in comparison with the control. In the study of the level of endothelin-1 in plasma, an increase in this indicator in MI in the early stages of the study was determined by 1.6 times in comparison with the control. Since one of the key roles in the development of dysfunction and endothelial destruction is assigned to the factors of oxidative stress, a correlation analysis of the relationship between the oxidative modification of fibrinogen and the parameters of endothelial function was carried out. A direct correlation was shown between the level of oxidized fibrinogen and the level of Endothelin-1 ($r = 0.78$, $p < 0.01$), and a direct correlation with the level of von Willebrand factor ($r = 0.365$, $p < 0.01$). Linear regression analysis confirmed the associations of oxidized fibrinogen with the indicated parameters of endothelial dysfunction. Also, a correlation analysis was carried out between the development of post-infarction depression and changes in the biochemical parameters of the blood of the examined people at different periods of the study. An inverse correlation was noted between the development of post-infarction depression and the level of fibrinogen ($r = -0.467$) and oxidized fibrinogen ($r = -0.514$), with the level of Endothelin-1 ($r = -0.373$) and von Willebrand factor ($r = -0.374$).

CONCLUSION

Based on the results obtained, it can be emphasized that with MI, in patients with

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developed DS, along with increased oxidative changes in lipids and plasma proteins, there is also a significant oxidative modification of fibrinogen, which does not depend on the concentration of fibrinogen. Oxidized fibrinogen potentiates potentially prothrombogenic changes in the vascular-platelet link of hemostasis, in particular, the acceleration of leukocyte-platelet aggregation. The revealed signs of thrombotic and hypercoagulant hemostasis disorders in patients with MI with depressive disorders, such as signs of endothelial dysfunction, elevated von Willebrand factor levels, are associated with oxidative changes in plasma fibrinogen in patients with MI with the development of DS, have a high diagnostic value.

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