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Effect of Lipid-lowering Therapy and Regular Exercise on the Fibrinolytic System in Patients with Metabolic Syndrome

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Abstract

At present, it has been established that in patients with a combination of the main components of the metabolic syndrome (arterial hypertension, dyslipidemia, abdominal obesity, insulin resistance), violations occur in many vital systems, including the hemostasis system. The effect of short-term (8-week) course of combination of lipid-lowering therapy and dose-related physical loads on the parameters of the fibrinolysis system in patients with metabolic syndrome was studied. It was shown that treatment with a combination of fibrates with physical loads is accompanied by a decrease in the level of fibrinogen and acceleration of fibrinolysis. The use of statins as hypolipidemic agents was accompanied by a reduction in the level of fibrinogen compared with fibrates and activation of fibrinolysis. Obviously, exercise exacerbates the mechanisms of action of hypolipidemic drugs on fibrinogen synthesis and fibrinolysis processes, which causes a favorable effect of their combined use.

Keywords: Metabolic syndrome; Hemostasis; Statins; Fibrates; Physical activity

Introduction

At present, it has been established that in patients with a combination of the main components of the metabolic syndrome (arterial hypertension, dyslipidemia, abdominal obesity, insulin resistance), disorders develop in many vital systems [1,2], including in the hemostatic system [3]. It was found that with the metabolic syndrome, the thrombogenic potential of the blood can be greatly increased [4,5]. In these patients, thrombus formation was increased and fibrinolysis was reduced [6]. Moreover, at present, a high level of the inhibitor of the tissue activator of plasminogen type 1, which contributes to the reduction of fibrinolytic activity of the blood, is already considered to be the main components of the metabolic syndrome [7]. All this contributes to the development of cardiovascular diseases, thrombosis in persons with metabolic syndrome [8,9].

There is information about the relationship between the components of the metabolic syndrome and pathological changes in the hemostatic system [10,11]. It is recognized that the basis of treatment of the metabolic syndrome is drug therapy [12,13], which affects all components of this pathological condition [14,15]. At the same time, it may be strengthened by non-medicamentous effects [16,17]. There is reason to believe [18,19] that such treatment will be able to exert a pronounced positive effect, including on the haemostatic parameters of the blood. The goal is to assess the influence of lipid-lowering drugs in people with metabolic syndrome on the background of regular physical activity.

Material and Methods

The conduction of the research was approved by the local Ethics Committee of the South-West state University in May, 25th, 2016 (Record №5) and the local Ethics Committee of the Kursk State University in May, 25th, 2016 (Record №7). All the examined persons gave written informed consent on participation in the conducted research. The study included 100 patients (48 men and 52 women aged 42 to 58 years) with metabolic syndrome. Inclusion criteria were the presence of hypertension (the level of systolic blood pressure was 160-179 mm Hg and/or diastolic blood pressure-95-109 mm Hg); dyslipidemia with elevated serum triglyceride concentrations of more than 180 mg/dl and/or low-density lipoprotein cholesterol greater than 160 mg/dL with a total cholesterol greater than 250 mg/dL; abdominal obesity, which indicated the value of the ratio of waist circumference to the hip circumference more than 0.95 in men and more than 0.8 in women; impaired glucose tolerance-the level of glucose in the serum of venous blood on an empty stomach to 120 mg/dL and 140-200 mg/dl 2 h after oral loading of 75 g of glucose; the presence of insulin resistance was established by the presence of at least one of the following indices: the level of insulin in the fasting serum >22 micro U/ml or the ratio of glucose (mg/dL)/insulin (μU/ml) in blood serum <6.0 fasting and/or 2 h after the oral load-75 g of glucose.

Patients were divided into two groups depending on hypolipidemic therapy: group 1 patients received fibrates for 8 weeks (micronized fenofibrate at a dose of 200 mg/day or etofibrate at a dose of 500 mg/day), and patients in group 2-statins (simvastatin in a dose 20 mg/day or lovastatin at a dose of 20 mg/day. At the same time as the fibrate and statin, the patients received physical activity daily in the form of athletics runs of 30 min per day.

In the blood plasma of patients, the concentration of fibrinogen and the lysis time of the clot of the euglobulin fraction of blood were measured. Blood plasma was obtained after centrifugation of venous blood, mixed in a ratio of 9: 1 with sodium citrate solution (0.11 M), at 1500 g for 10 min.

The level of fibrinogen was determined by the method of Klaus by the time of clot formation in response to the addition to a dilute 10-fold plasma solution of thrombin. Fibrinolytic activity was assessed by the time of spontaneous lysis of the clot formed by the euglobulin fraction of the blood plasma in response to the addition of 0.025 M calcium chloride solution [20]. The parameters of fibrinolysis were recorded twice: initially and after 8 weeks of therapy.

The results of the study were processed using the "Statistica" software package. The data in the tables are presented as mean arithmetic mean values and errors of the mean (M ± m). The reliability of differences was calculated using Student's t-test. Differences were considered reliable at $p<0.05$.

Results and Discussion

Analysis of fibrinolysis in patients with metabolic syndrome revealed a marked increase in the level of fibrinogen in the blood and inhibition of fibrinolysis. Table 1 presents data on the effect of fibrates (group 1) on the background of physical loads on the fibrinolysis system in patients with metabolic syndrome. A statistically significant decrease in the fibrinogen concentration in the blood was observed only in patients of group 1-1 and 1-2, who received fibrate for 8 weeks and received physical exertion. The fibrinolytic activity against the background of this therapy also increased. The use of fibrates without physical exertion did not exert significant influence on the considered indices (Table 1).

Group/treatment	Fibrinogen, g/l		Clot lysis time, min	
	initially	8 weeks of treatment	initially	8 weeks of treatment
1-1. Fenofibrate + physical exercise	4.7 ± 0.09	2.6 ± 0.12**	362.6 ± 0.71	320.2 ± 0.69*
1-2. Etofibrate + physical exercise	4.9 ± 0.13	2.8 ± 0.16**	380.2 ± 0.83	318.6 ± 0.75*
1-3. Fenofibrate	4.6 ± 0.16	4.2 ± 0.14	391.1 ± 0.73	344.2 ± 0.63
1-4. Etofibrate	4.8 ± 0.10	4.3 ± 0.11	386.2 ± 0.65	339.6 ± 0.54

Table 1: Parameters of fibrinolysis before and after an 8-week course of fibrate therapy on a background of physical activity.

It is known that most fibrates possess an antithrombogenic effect due to a decrease in fibrinogen concentration. In vivo experiments in laboratory animals, fibrolic acid derivatives inhibit the synthesis of fibrinogen, reducing the concentration of matrix RNA for the chains of the fibrinogen molecule in the liver [21]. However, the literature data on the effect of fibrates on fibrinolysis are ambiguous. Thus, in a number of studies it has been shown that fibrates, along with a decrease in fibrinogen concentration, also increase fibrinolytic activity [22]. However, other works do not confirm this [23].

According to modern ideas, the mechanism of action of fibrates is mainly related to their effect on the transcription of genes involved in the metabolism of lipoproteins [23]. It is believed that fibrates are ligands of nuclear receptors activated by the peroxisomal proliferator), by binding to which they stimulate the lipolysis of enriched triglycerides of lipoproteins (activation of lipoprotein lipase and inhibition of the production of its inhibitor-apoprotein) and cholesterol reverse transport in high-density lipoproteins (activating the synthesis of apoproteins AI and All and the ABCA1 receptor) [11]. It has also been found that fibrates can reduce the expression of the gene that codes for the synthesis of fibrinogen, which is accompanied by its decrease in blood plasma [24].

In the study, both fibrates showed a comparable positive effect on the fibrinolysis system against the background of physical exertion. This makes it possible to consider their combination with physical loads successful from the point of view of simultaneous correction of interrelated metabolic disturbances in persons with a metabolic syndrome.

Table 2 presents the results of an 8-week treatment of patients with metabolic syndrome with drugs from the class of statins (group 2) in combination with the same physical loads. In groups of patients who received physical exercises along with statin (groups 2-1 and 2-2), a significant dynamics of all investigated parameters of fibrinolysis was revealed. At the same time, the isolated use of simvastatin or lovastatin did not lead to a decrease in the time of spontaneous lysis of the blood clot during the observation period (Table 2).

Group/treatment	Fibrinogen, g/l		Clot lysis time, min	
	initially	8 weeks of treatment	initially	8 weeks of treatment
2-1. Simvastatin+physical exercise	4.9 ± 0.12	2.6 ± 0.21**	361.0 ± 0.65	305.7 ± 0.73*
2-2. Lovastatin+physical exercise	4.7 ± 0.15	3.0 ± 0.25**	402.3 ± 0.80	320.1 ± 0.69*
2-3. Simvastatin	4.8 ± 0.21	4.3 ± 0.19	388.6 ± 0.78	358.4 ± 0.63
2-4. Lovastatin	4.6 ± 0.18	4.2 ± 0.15	383.2 ± 0.75	349.1 ± 0.79

Table 2: Parameters of fibrinolysis before and after the 8-week course of combined therapy with statins on the background of physical activity.

The effect of statins on the hemostasis system is being studied rather actively; however, the results of the studies are ambiguous. Some studies report data on the stimulation of fibrinolysis and/or the reduction of thrombotic potential in patients with cardiovascular disease in the presence of statin therapy [23], in other studies, these data are not confirmed [24].

Previously, the effect of simvastatin and atorvastatin on the parameters of hemostasis in patients with coronary heart disease with hyperlipidemia and type 2 diabetes mellitus was studied [25]. It was shown that the therapy of these patients with simvastatin or atorvastatin within 12 weeks caused normalization of the lipid spectrum and reduced the high level of fibrinogen and the activity of

factor VII of blood clotting. Apparently, the positive effect of statins on the thrombogenicity of patients' blood is due to a decrease in the concentration of large particles of very low density lipoproteins enriched in triglycerides [18]. Previously, a positive correlation between the concentration of triglycerides in the blood of patients with dyslipidemia and the level of inhibitor of fibrinolysis of the inhibitor of tissue plasminogen activator-1 was shown [26]. Previously, the pleiotropic effects of statins, in particular, on the hemostatic system, which manifest themselves regardless of their basic properties associated with a decrease in the level of lipids [27]. This was confirmed in an experiment [28]. Apparently, statins, regardless of the effect on the synthesis of cholesterol, reduce the level of geranylgeranil pyrophosphate, which activates the low-molecular G-protein Rho involved in the synthesis of tissue plasminogen activator inhibitor at the level of transcription. In addition, the activation of the Rho protein under the influence of statins leads to enhanced expression of the tissue plasminogen activator by endothelial cells [23]. As a result of the use of statins, the ratio of the main regulators of fibrinolysis, fibrinolytic activity increases. This effect is greatly enhanced against the background of regular, ordered muscular activity. The manifestation of the positive effect of lipid-lowering drugs on the hemostasis system was observed against the background of daily athletics runs. It is known that the appointment of physical regular loads in the feasible mode can itself have a positive effect on the hemostatic system, reducing the prothrombotic state of cardiac patients [29,30,31]. Given the existence of pathophysiological interrelations among the components of the metabolic syndrome, it can be assumed that the contribution to the reduction of thrombogenic blood potential in such patients is due to the potentiation of the positive effects of lipid-lowering drugs on the basic metabolic processes by physical loads.

Conclusion

It has now been found that developing disorders in many vital systems are accompanied by dysfunctions of hemostasis in patients with a combination of the main components of the metabolic syndrome (arterial hypertension, dyslipidemia, abdominal obesity, insulin resistance). In the study, the effect of a short-term (8-week) course of combining lipid-lowering therapy and dose-related physical activity on fibrinolysis activity in patients with metabolic syndrome was studied. It was found that treatment with a combination of fibrates with physical loads is accompanied by a pronounced decrease in the level of fibrinogen and acceleration of the fibrinolysis process. The use of statins as hypolipidemic agents provides a fibrate-comparable level of fibrinogen and the degree of fibrinolysis activation. It became clear that exercise increases the effect of hypolipidemic drugs on fibrinogen synthesis and fibrinolysis processes, which makes this combination very preferable.

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