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Evaluation of blood prothrombotic parameters under the influence of physical activity

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Abstract

Introduction. *Blood is a suspension of cellular components in plasma. Its viscosity is affected by haematocrit, the aggregation ability of erythrocytes and the viscosity of plasma, conditioned by high-molecular fibrinogen proteins or lipoprotein. The increase of blood viscosity occurs in the course of many diseases leading to the formation of atherosclerotic lesions.*

Material and methods. *The study involved 50 patients with femoral-popliteal type of occlusion in stage IIB according to Fontaine's classification. Before the training, the patients underwent a treadmill test evaluating claudication distance. The proposed training included physical exercise performed 3 times a week and lasting 30 minutes for a period of 6 months. Before and after the training, venous blood samples for laboratory tests were taken to determine the values of haematocrit, haemoglobin, as well as phosphatase and calcium D-dimers. The purpose of the study was to evaluate the impact of training on selected blood rheological parameters. In addition, the change in BMI values and the length of distance of relative claudication were evaluated in the prospect of changes in laboratory values.*

Results. *The applied training contributed to the reduction of selected blood parameters. Statistical significance was observed at $p < 0.0001$ for D-dimers, haematocrit and phosphatase. The changes in BMI values were reflected in the results of D-dimers and phosphatase. A statistical significance also occurred in the case of the extension of claudication distance and changes in the values of D-dimers, haematocrit and phosphatase.*

Conclusions. *The supervised training had an impact on the reduction of prothrombotic blood parameters. Health-oriented physical exercise can contribute to body weight decrease and painless distance extension.*

Key words: blood, D-dimers, training, body weight

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Introduction

The atherosclerosis of lower limbs is a disease process whose symptoms increase with the passage of time. Its progression occurs in as many as 16% of patients. Surgical procedures are necessary for 7% of patients and end in amputation for 4%. The location of lesions is also important. It turns out that the patients with stenosis of the final section of the aorta have a worse 5-year survival rate than those suffering from femoral artery stenosis. High mortality rate is associated with the risk of cardiovascular disease, and diabetes negatively affects the prognosis.

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The biggest medical problem for doctors and physiotherapists is impaired walking economy and restriction of walking due to pain. The affected patients walk slower, are more oriented on gait stability than pace and make shorter steps. Such a lack of ergonomics makes the oxygen cost appropriate for walking a given distance greater in percentage rates than in normal conditions. Maximum oxygen consumption is limited not only due to atherosclerosis or inactivity, but also because of frequent comorbidities or overweight. Brzostek et al. [1] have shown that cigarette smoking reduces exercise capacity more than coronary artery disease or diabetes. These patients' ABI indicator correlates with their low physical activity [1].

A very important element of conservative treatment is physical activity in patients in the second stage, according to Fontaine's classification, and after surgery treatments. During the analysis of numerous exercise rehabilitation programmes, Gardner and Poehlman [2] demonstrated that the following aspects are important to achieve the most beneficial treatment of patients with intermittent claudication: end point of claudication pain (absolute claudication); duration of training session, which should be longer than 30 minutes and repeated at least three times a week; type of effort, i.e. walking. It has been proved that walking under the supervision of a doctor or physiotherapist improves physical condition more than training in an outpatient environment, which is likely due to the lack of discipline of the patient. In addition, physical exercise, especially walking, reduces the risk of death, as confirmed by the study of Hiatt et al. [3]. It is probably related to the application of cardiovascular adaptation mechanisms, including the impact on blood pressure, lipid profile and coagulation mechanisms. The reduction of symptoms of intermittent claudication in patients with atherosclerosis of lower limbs results from multiple reactions to physical training. It is worth mentioning here the adaptation or redistribution of peripheral blood flow, inhibition of the progression of atherosclerosis, blood rheology and metabolic changes, changes in skeletal muscle morphology, economisation of walking, pain perception and impact on the cardiovascular system [4, 5].

The disorders of homeostasis and endothelial function are often accompanied by atherosclerosis of lower limbs. Impaired fibrinolysis is considered to be one of the factors involved in the development of thrombotic complications. The activity of endothelial damage markers and increased blood clotting facilitate the platelets to adhere (adhesion) to the arterial wall. At the same time, they play a key role in the formation and progression of dangerous atherosclerotic plaques. Another fibrinogen decomposition product is D-dimers, which have a high sensitivity in the diagnosis of thrombus. Their partial decay time is estimated at 8 hours. They have anticoagulant properties and appear in the form of secondary activation of fibrinolysis (after the activation of coagulation). As a result of complex mechanisms operating within a fibrinolytic system, all the above factors are of great importance in the process of angiogenesis.

Material and methods

The study group included the patients suffering from ischaemia of lower limbs in stage IIB, according to Fontaine's classification, and hospitalised in the University Hospital in Wroclaw. We analysed only those patients who suffered from the lack of blood supply to the extremities of femoral-popliteal closure type. Fifty patients with claudication symptoms appearing before 200 metres were qualified into the group.

The study excluded the patients with:

- trophic changes in the lower limbs;
- sensory disturbances resulting from ischaemia (sensory neuropathies) without claudication symptoms;
- comorbidities that permanently impaired motor functions;
- comorbidities that are a contraindication to the exercise test;
- diagnosed mental illness;
- lack of informed and voluntary consent to participate in the study.

All the patients surveyed underwent the test specifying intermittent claudication (Treadmill Stress Test), where the treadmill moved at a constant speed, i.e. 3.2 km/h with a 10-degree running area angle.

The study group participated in aerobic exercises — Nordic Walking with 80% individual relative claudication intensity. Its determination was preceded by physical effort programming. The patients undertook the training indicated for them for a period of six months — 30 minutes three times a week.

Before the tests, the respondents completed the questionnaire covering the socio-demographic structure of the studied groups, their age, education and place of residence. The symptoms of the disease, its duration and current treatment history were analysed.

To determine the cellular blood parameters, such as haemoglobin, haematocrit, total calcium, platelets, phosphatase and D-dimers, qualified medical personnel took venous blood samples from the study population. The studies were repeated after six months.

Statistical analysis

Conventional parametric and non-parametric tests were used in the statistical analysis of the material used, depending on the nature of variables (discrete or continuous) and their empirical distributions. Single-fac-

Table 1. Characteristics of the study group

Variables		N	%
Gender	Women	12	24%
	Men	38	76%
Age	46–55	7	14%
	56–65	21	42%
	> 65	22	44%
Comorbidities	Diabetes	21	42%
	Hypertension	30	60%
	Stroke	5	10%
	Myocardial infarction	8	16%
	Hypercholesterolaemia	1	2%

tor analysis of variance (ANOVA) and non-parametric Kruskal-Wallis ANOVA test were used. The comparative analysis of the two distributions was performed using parametric t-Student test for normal distributions or its non-parametric equivalent — U Mann-Whitney test — in case of distributions significantly deviating from the normal distribution.

The purpose of the study was to evaluate the impact of training on selected blood rheological parameters. In addition, the change in BMI values and the length of distance of relative claudication were evaluated in the prospect of changes in laboratory values.

Results

The characteristics of the study group in terms of gender, age and comorbidities are shown in Table 1.

When analysing the age ranges of the study group, it can be concluded that the respondents after 66 years of age were dominant. An equally large group was the patients aged 56–65. It is worrying that 14% of subjects suffering from pain caused by physical exercises were aged less than 55. It indicates the presence of relatively early signs of atherosclerosis of lower limbs and the rapid progression of the disease (Table 1). The average age for men was 64.4 ± 6.0 years and for women 62.7 ± ± 6.9 years.

When analysing the gender of the patients qualified for the study, it can be concluded that men (76%) are dominant in the group. Statistical differences concern the diversity in terms of gender, in a group of ill patients (χ^2 (df = 2) = 16.44, p = 0.0003).

The most frequent comorbidities in patients with lower limb ischaemia include: diabetes (42%), hypertension (60%), myocardial infarction (16%) and stroke (10%).

The analysis of the results of laboratory tests in the study group

As part of the diagnosis of chronic ischaemia of lower limbs, in addition to finding common symptoms such as pain of lower limbs, reduced temperature and reduced muscle strength, laboratory tests are performed. In the study population, the level of blood platelets, haemoglobin, D-dimers, haematocrit, phosphatase and total calcium were taken into account. The choice of these variables is justified. They are responsible for the process of initiation of coagulation, fibrinolysis and vasoconstriction. In the place of endothelial damage, which may occur in the lower limb vessels, the accumulating platelets lead indirectly to the formation of clots cutting off blood supply to tissues. Coagulation and fibrinolysis mechanisms are initiated, among others by D-dimers. Their level increases among the elderly and people with low physical activity. A correlation between D-dimers and fibrinogen (acute phase protein) indicates the relationship between thrombosis and inflammation posing a risk factor for cardiovascular diseases.

The elevated level of haematocrit indicates excess of erythrocytes and dehydration, causing blood to be thicker. This in turn favours the formation of blood clots tapering the lumen of the vessel.

The function of the vessel including, among others, blood transfer, can be impeded by the rigidity of the walls, resulting from excessive deposition of calcium [6].

When observing the average values of the parameters before and six months after the training, their decline is noticeable. Particularly important changes are noticed for haemoglobin (from 13.92 to 13.05 g/dL); D-dimers (from 0.90 to 0.44 μg/mL) and haematocrit (from 41.94 to 38.63%).

The results of blood tests were analysed using a post hoc test, which gave the opportunity to indicate the mean pairs differing significantly. The impact of training on the differences of the studied laboratory parameters: haemoglobin, D-dimers, haematocrit and phosphatase in the study group was found to be statistically significant $p < 0.001$. This allows confirming the thesis about the positive effect of physical activity on blood parameters (Table 2).

The length of the distance covered was dependent on the gender — in women walking distance was on average shorter by 14 metres shorter than men. The positive fact is that the distance increased in both groups after a 6-month training: in women the distance increased by 20 meters and in men — by 30 meters. It is a good prognostic sign for supervised physical exercises.

When analysing the changes in blood parameters and the distance covered by the patient until the first

Table 2. Laboratory parameters in the study group before and after the training

Measurement	Before the training		After 6 months		ANOVA	
	Average	Standard deviation	Average	Standard deviation	F	p
Platelets [K/uL]	233.0	61.6	249.3	52.9	1.21	0.3011
Haemoglobin [g/dL]	13.92	0.99	13.05	1.11	9.83	**0.0001**
D-dimers [g/mL]	0.90	0.95	0.44	0.21	9.58	**0.0001**
Haematocrit (%)	41.94	2.87	38.63	3.17	10.96	**< 0.0001**
Total calcium [mg/dL]	9.94	0.32	9.87	0.35	1.44	0.2402
Phosphatase [U/L]	82.0	18.1	74.6	22.7	3.58	**0.0079**

Table 3. The relationship between selected laboratory parameters and claudication distance before and after the training

Measurement	ICD before the training			ICD after six months		
	ρ-Spearman	t	p	ρ-Spearman	t	p
Platelets [K/uL]	0.04	0.29	0.774	0.06	0.39	0.701
Haemoglobin [g/dL]	–0.08	0.54	0.392	–0.10	0.68	0.499
D-dimers [g/mL]	–0.09	0.61	0.445	–0.03	0.19	**0.009**
Haematocrit (%)	0.10	0.72	0.345	0.10	0.71	**0.012**
Total calcium [mg/dL]	–0.21	1.50	0.140	–0.10	0.67	0.507
Phosphatase [U/L]	0.11	0.78	0.141	0.09	0.60	**0.034**

ICD — intermittent claudication distance

symptoms of ischaemia (assuming statistical significance at $p > 0.05$) significant differences were found for D-dimers ($p = 0.009$), haematocrit ($p = 0.012$) and phosphatase ($p = 0.034$). For the remaining parameters, there was no significant difference between the covered distance (after 6 months) and the values of blood rheology parameters (Table 3).

Exercise training-induced weight loss significantly influenced the selected laboratory parameters in the study population. A significant correlation was found between the levels of D-dimer ($p = 0.295$) and phosphatase ($p = 0.338$). This study confirms the assumption that overweight is detrimental to the human body, because it predisposes to metabolic, vascular and musculoskeletal system diseases, and the supervised physical exercise training decreases the risk by reducing the levels of prothrombotic parameters.

Discussion

The alarming fact is that more than 60% of adults worldwide do not perform physical activity. The project entitled 'Bridging the East-West Gap' has shown that Poland is among the countries with the lowest percentage of people doing sports in their free time. Almost 73% of adult Poles said they had not been doing any physical exercises. We should not forget that physical activity is one of the most important and modifiable risk factors for many diseases. Epidemiological data show that lack of exercise and smoking also account for 75% of cases of coronary heart diseases. Framingham study has shown that an increase in energy expenditure by about 1000 kcal per day may cause a decrease in the overall mortality rate by about 30%, and the people who actively spend their time, live on average two years longer [7–9].

Laboratory studies often enrich the diagnosis and supplement in some way the conclusions arising from the studies. The changes in blood rheological parameters in patients with atherosclerotic occlusive artery disease of lower limbs are not a novelty for the medical community. Turczynski et al. [10] assessed the relation between physical activity and biochemical parameters of the blood. The authors evaluated blood and plasma viscosity, as well as their effect on the distance of intermittent claudication in patients with ischaemia of lower limbs. The results showed a significant increase in blood (by about 23%) and plasma (11%) viscosity, as compared with the control group. Additionally, haematocrit level was higher by 7.5% and the blood viscosity correlation with haematocrit was very high ($r = 0.84$; $p < 0.001$). Taking into account the associa-

tion of these results with claudication, it was proved that the correlation was negative, which means that high blood viscosity values were present mostly in people reaching smaller distances of intermittent claudication. These types of disorders are typical for patients suffering from atherosclerosis. The increase in haematocrit is noteworthy, as it also has a direct impact on blood viscosity [11, 12].

The study demonstrated that claudication distance change has significantly influenced the change in blood rheological parameters: D-dimers, haematocrit and phosphatase. The results have proved to be significant only for these variables. No statistical significance was observed for other values.

The first researcher who drew attention to the increase in blood viscosity in patients with peripheral artery disease was Dormandy et al. [13]. He associated the increase in blood viscosity only with the increased level of fibrinogen. The results were confirmed by other authors in later years. Some additional changes were also noticed, i.e. the increase in haemoglobin level, decreased susceptibility of erythrocytes to deformation, as well as increased platelet and haematocrit aggregation. One of the many determinants of atherosclerotic disease and its progression is blood rheological changes. The study of Turczynski et al. [11] have shown a negative relationship between the perfusion of affected tissues and blood and plasma viscosity. Therefore, the presence of resistance components in energy dissipation in patients with limb ischaemia plays an important role [10, 14, 15].

Obesity has a little impact on blood viscosity changes. In the general population, obesity increases with age, suggesting deterioration of the mechanisms of self-regulation of rheological parameters in the aging process. In summary, Turczynski [11] and many other authors have considered abnormal blood rheology and, especially, the increased plasma viscosity as one of the major risk factors for atherosclerosis [11, 16, 17].

The author examined the effect of body weight on blood biochemical parameters before and after the training. There was a significant relationship between the levels of D-dimer ($p = 0.295$) and phosphatase ($p = 0.338$). The examination confirmed the assumptions that overweight is detrimental to the human body, predisposing to metabolic, vascular and musculoskeletal system diseases.

The analysis of the results of blood tests before and after the supervised training was performed using 'post hoc' test, which enables the identification of the mean pairs differing significantly. The tested laboratory parameters: haemoglobin, D-dimers, haematocrit and phosphatase showed significant differences between the mean values after the training at $p < 0.0001$. It allows confirming the thesis about the positive effects of physical activity on blood laboratory parameters.

Authors' own studies have confirmed that the age range between 45 and 55 years is characterised by the highest values of haemoglobin, haematocrit, D-dimers and phosphatase. The increase in haemoglobin and haematocrit concentrations indicates an increased density of blood. These changes in blood rheological properties lead to the formation of blood clots and, as a consequence, to the closure of the lumen of the vessel. An important factor was the earlier introduction of preventive measures to prevent the development of disease [9, 18].

Although the body is equipped with mechanisms to maintain homeostasis of rheological parameters of the blood, they often fail. Still, there is a possibility of their correction [19].

Physical activity was not satisfactory among study participants before the planned training. As many as 36% (18 patients) in the group declared that they would not engage in recreational activities. The most commonly referred physical activity was cycling, cited as a recreational activity practiced before the symptoms associated with limb ischaemia occurred [8, 20].

Ponikowska and Kowalewska's studies [21] have shown the benefits of training in patients with atherosclerosis of lower limbs. The results of the subjective assessment of the respondents revealed the decrease of the symptoms of cold and numbness in the extremities. The average distance increased more than three times, gait efficiency improved and the duration of pain shortened from 18 to 11.3 seconds [21, 22].

It should not be forgotten that all the activities promoting physical activity also affect social relationships. Both physical exercises and walking have a positive effect on the vascular system. Additionally, people can make new friendships, share common interests and spend free time together [12, 23].

Conclusions

1. The conducted study confirmed the positive impact of supervised training on the rheological properties of blood through their reduction, as was the case with D-dimers, haematocrit and phosphatase at $p < 0.0001$.
2. Regular physical activity increased the average claudication distance by 30 metres among men and by 20 metres among women in the study group. The extension of painless distance achieved has considerably influenced the significance of blood parameters; D-dimers ($p = 0.009$), haematocrit ($p = 0.012$) and phosphatase ($p = 0.034$), with $p < 0.05$ considered as statistically significant.

3. Reduction in body weight significantly correlated with the values of D-dimers and phosphatase, confirming the beneficial effect of supervised physical activity in patients with ischaemia of lower limbs.

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