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Control of Blood Microcirculation Parameters in Therapy with Alpha-Lipoic Acid in Patients with Diabetes Mellitus

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Abstract—In this study, we assessed the possibility of using portable laser Doppler flowmeters for determining the state of the blood microcirculatory system in upper and lower limbs of diabetic patients during the treatment course with intravenous α-lipoic acid infusions. A series of experimental studies were conducted in a cohort of ten inpatients with a confirmed diagnosis of type 2 diabetes mellitus. The state of peripheral blood flow of patients was assessed during 5 days on which they received daily doses of intravenous α-lipoic acid infusions. The values of the microcirculation and nutritive blood flow indices, as well as the bypass index, were assessed. To obtain a more extensive analysis, the patients' measurement results were compared with those of the control group composed of ten conditionally healthy volunteers of similar age. To determine changes in the regulatory mechanisms for the microcirculatory bed, we applied the amplitude-spectrum analysis of microvascular blood flow oscillations, using the mathematical tool of wavelet transform. We determined the changes in the index of blood microcirculation and the parameters of microcirculatory blood flow distribution into nutritive and shunt pathways, as well as the differences between these changes in upper and lower limbs. This approach is believed to become prospective as a pharmacotherapy efficacy assessment method based on responses of the system of blood microcirculation.

Keywords: noninvasive diagnostics, diabetes mellitus, laser Doppler flowmetry, blood microcirculation, intravenous infusions, α-lipoic acid, portable microcirculation analyzer

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INTRODUCTION

One of the leading causes underlying the invalidation and increased mortality of patients with diabetes mellitus (DM) is the development of its concomitant complications. The DM complications are subdivided into acute and chronic ones, such as diabetic nephropathy, retinopathy, and microangiopathy, etc. Some previous studies have shown that the lifespan and the quality of life in patients with DM depend, to a considerable degree, on the presence and the degree of expressiveness of its chronic complications [1]. Diabetic polyneuropathies (DPNs) are one of the most frequent DM complications, as well as the world's leading cause of nontraumatic extremity amputations. In addition, DM is related to the group of the main causes for neuropathy development around the world, especially, in industrially developed countries. Its statistics shows that from 30 to 50% of DM patients develop DPNs within their lives [2]. This aggravation is characterized by a complicated pathogenic network of mutually bound metabolic, neurotrophic, and vascular deficiencies, which lead to chronic progressive lesions and the loss of nonmyelinated and myelinated peripheral nerve fibers [3]. Thin fibers predominantly suffer in DPN development, including sympathetic fibers sustaining tonus in arteries and arterioles and sensory peptidergic fibers stimulating vasodilation. The growing DM morbidity (International Diabetes Federation (IDF) Diabetes Atlas, 9th ed. [electronic resource], 2019; URL: https://www.diabetesatlas.org, accessed: 28.10.2021) is one of the most important problems for contemporary healthcare. Novel strategies are required for the early diagnosis and effective treatment of DM complications, as well as for their prophylaxis.

Laser Doppler flowmetry (LDF) is an optical noninvasive technology successfully applied over many years in the clinical practice of pathologies associated with dysfunctions in microvascular blood flow. One of the fields successfully applying this method is, in particular, the diagnostics of micro- and macrovascular

Table 1. Main clinical and laboratory indicators in the patients

No.	Indicator	Value
1	Gender (M/F)	4/6
2	Age, years	56 ± 14
3	Body mass index, kg/m^2	32.0 ± 6.8
5	Disease duration, years	14 ± 7
6	Systolic pressure, mm Hg	142.0 ± 22.1
7	Diastolic pressure, mm Hg	82.5 ± 6.3
8	Fasting glucose, mmol/L	15.2 ± 7.0

dysfunctions developing in DM patients in the course of their lives [4–7].

The important and advantageous specificity of LDF, compared to other methods of studying blood microcirculation (BMC), is related to its capacity to obtain not only general volumetric blood flow data, but also important diagnostic information on the microvascular bed and its regulation by the organism's different systems, including nervous and humoral regulation. The recorded LDF signal can be divided into its components, using the wavelet analysis [8]. Thus, we can evaluate the endothelial, neurogenic, and myogenic regulation values, as well as those of pulse and respiratory waves.

Since LFD has proven itself as a well-recommended method in many medical fields associated with BMC dysfunctions, the idea of its variant as a portative device for personalized application and noninvasive diagnostics is now gaining significance. Over the last few years, Russian researchers have developed portable LDF analyzers operating without optic fiber and translating measurement data to PCs through Bluetooth or Wi-Fi protocols [9, 10]. These analyzers may possibly be used for organizing a distributed system of flowmeters to synchronously control BMC in several regions of the body (up to 6 investigation areas.). These analyzers have already demonstrated their positive application potential in studies involving different age groups of healthy volunteers [11, 12], and volunteers of different smoking status [13] and studies of BMC differences between different regions of the body, depending on changes in its spatial position [14], but their present application in clinical DM management is not so widespread [15].

One of the prospective areas for the application of novel portable LDF devices in the clinical practice of DM is related to the treatment efficacy assessment in the therapy of its complications. The stationary LDF monitors were already used to assess the diabetic polyneuropathy symptoms against taking, in particular, different doses of vitamin D [16]. Since oxidative stress is thought to be one of the leading causes for developing complications in DM [17], antioxidant therapies are frequently applied in their therapy. Some previous studies have shown a possibility to decelerate and even inhibit the development of diabetic complications by using an antioxidant therapy at early stages [18]. The group of strong antioxidants used in the therapy of DM complications includes α-lipoic (ALA), or thioctic acid.

ALA was reported to possess a sum of potentially useful effects in both the prophylaxis and the treatment of peroxidation-associated diseases. The studies devoted to the application of ALA in the management of DM complications have shown that it contributes to weight reduction in obesity [19] and increases insulin sensitivity in DM patients [20]. The ALA-involving therapy finds its most frequent application in diabetic neuropathy. Numerous studies in this field have shown that this therapy can significantly decrease the degree of expressiveness in symptomatic diabetic polyneuropathy [21–24]. Despite all the above listed positive effects of ALA, the data reported in the studies devoted to the effects of treatment courses involving this substance are still insufficient for making definite conclusions on changes in the functions of vessels and the state of BMC.

The purpose of this study was to investigate, using a distributed system of new portable LDF analyzers, a simultaneous response of the blood microcirculation system from several regions of the body to the course of intravenous infusions of the ALA solution administered to DM patients. The tasks of the study were to evaluate the possibility and prospects for the application and implementation of the LDF method as portable devices of instrumental diagnostics for assessing therapeutic efficacy in the treatment of disorders associated with blood microcirculation dysfunctions, as well as to carry out an integrated and extensive study of changes in the BMC parameters in DM patients in the course of treatment based on intravenous infusions of ALA solution.

METHODS

The study participants included ten inpatients of the Endocrinology Department of the Orel Regional Clinical Hospital (Orel) with confirmed diagnosis of type 2 diabetes complicated by diabetic polyneuropathy of upper or lower limbs. The study did not include patients with diabetic foot syndrome in anamnesis, as well as those in the acute period of diseases associated with the cardiovascular and bronchopulmonary systems, gastrointestinal tract, liver, kidneys, blood, which could interfere with the accuracy of diagnostic results. Patients with anamnestic history of alcoholism and drug addiction were excluded from the study. The main clinical and laboratory indicators in the investigated patients with endocrine profiles were measured in accordance with standard laboratory procedures (Table 1).

All measurements were conducted at least 2 h after the most recent food intake in the first half of the day.

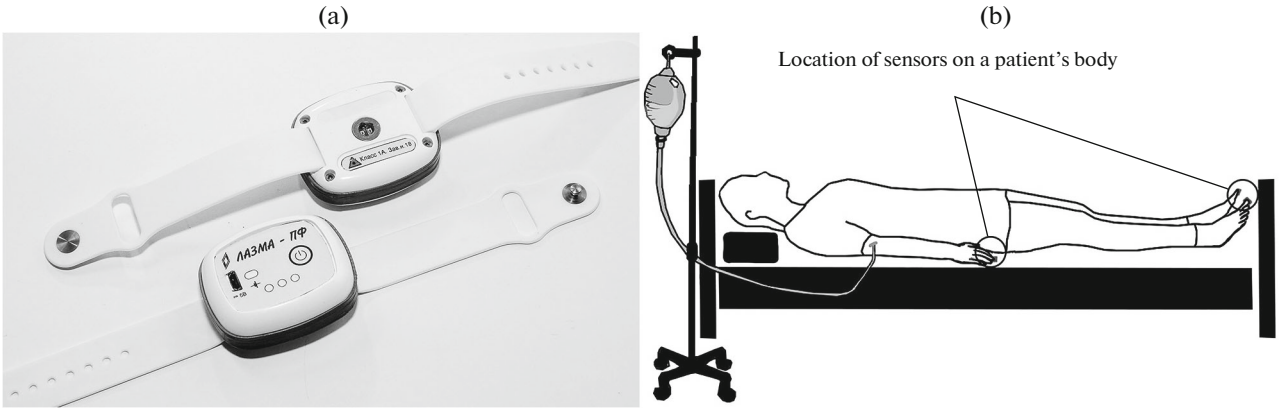

Fig. 1. The image of portable LAZMA PF (a) analyzers and their schematic position on a subject's body under investigation (b).

Patients under the study were in a lying position in a calm physical and psychological state.

To assess the state of the microcirculatory bed in patients' upper and lower limbs, the experimenters applied a distributed system consisting of four portable LAZMA-PF laser Doppler analyzers (SPE LAZMA Ltd., Russia) allowing them to record the LDF signal synchronously in several regions of the body (the image of the applied devices is given in Fig. 1a). The probing wavelength of the LDF channel's emission constituted 850 nm in these devices, with the optic emission power not exceeding 1 mW at the output of the analyzer. Under investigation procedures, devices were fixed to the palmar surface of the patients' third finger and on the plantar surface of their first toe. The location of analyzers on a patient's body under the study is imaged in Fig. 1b.

In the course of inpatient treatment, each participant was prescribed a treatment scheme consisting of 5 intravenous infusions of ALA diluted at 600 IE per 200 mL of physiological saline solution. The ALA solution was introduced to the lateral subcutaneous vein of the right or the left hand, which was based on the choice of optimal vascular access, the state of peripheral veins at the site of injections, and a patient's individual preferences. The measurement procedure cyclogram is given in Table 2.

Thus, each patient participating in the study was examined five times for 6 days, starting on the 2nd inpatient day. Under each investigation procedure, experimenters recorded four LDF signals from upper and lower limbs for 10 to 20 min. The first three recordings were made on the first day of the study (i.e., on inpatient day 2). The recordings were made immediately before (for 10 min), during (for 20 min), and immediately after (for 10 min) the intravenous infusion of ALA. The next recording (for 10 min) was made on the next day, immediately before the second intravenous infusion of ALA, and the last recording (for 10 min) was performed on inpatient day 7, i.e., on the day after the last intravenous infusion of ALA solution.

During the LDF procedure, changes in the BMC index were recorded in time. The parameters to be assessed included the mean microcirculation index value (I_m, PU) in each investigation stage, mean squared deviation (MSD) of I_m–σ, in perfusion units (PUs), and the coefficient of variation K_v, %, calculated as the ratio between the MSD and mean I_m, value in percentage. The wavelet-analysis of the

Table 2. Cyclogram of measurements in patients

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	...	*n*-day
Hospital admission	1st infusion	2nd infusion	3rd infusion	4th infusion	5th infusion			Discharge from hospital
	Measurements: before infusion, 10 min; during, 20 min; after infusion, 20 min	Measurements: before infusion, 10 min				Measurements: in the morning, 10 min		

Table 3. Measurements results in the patient group, using portable LDF analyzers

Parameter	Fingers		Toes	
	before the start of the course	after completion of the course	before the start of the course	after completion of the course
I_m, perfusion units, PU	19.94 ± 6.45	16.84 ± 5.73	22.32 ± 5.99	19.13 ± 6.79
σ, PU	2.16 ± 0.96	1.85 ± 0.49	2.11 ± 0.73	2.04 ± 0.65
C_v, %	12.78 ± 8.48	13.24 ± 9.25	10.74 ± 5.84	11.82 ± 4.80
E, PU	1.08 ± 0.55	1.06 ± 0.51	0.82 ± 0.53	0.66 ± 0.56
N, PU	1.04 ± 0.48	1.05 ± 0.40	0.82 ± 0.51	0.57 ± 0.42
M, PU	0.75 ± 0.34	0.71 ± 0.28	0.60 ± 0.28	0.45 ± 0.20
D, PU	0.47 ± 0.13	0.44 ± 0.14	0.44 ± 0.05	0.43 ± 0.17
C, PU	0.72 ± 0.29	0.93 ± 0.55	0.77 ± 0.45	0.82 ± 0.72
E/3σ, rel. U, RU	0.20 ± 0.16	0.22 ± 0.17	0.13 ± 0.06	0.11 ± 0.08
N/3σ, RU	0.19 ± 0.13	0.21 ± 0.14	0.13 ± 0.06	0.10 ± 0.06
M/3σ, RU	0.12 ± 0.04	0.14 ± 0.07	0.10 ± 0.05	0.08 ± 0.06
BI, RU	2.41 ± 1.09	3.00 ± 1.93	2.64 ± 0.84	3.17 ± 1.79
I_{mn}, PU	8.86 ± 3.67	7.44 ± 5.21	9.35 ± 3.92	7.74 ± 4.69

recorded LDF signals was also made using mathematical software for portable LDF monitors. Oscillations were assessed in the endothelial (E, PU), neurogenic (N, PU), myogenic (M, PU), respiratory (R, PU) and pulse (P, PU) ranges, as well as the amplitudes of active range oscillation values normalized by MSD (E/3σ, N/3σ, and M/3σ, RU). The bypass index (BI, RU) and nutritive blood flow (I_{mn}, PU) values were assessed based on the determined ratios [25].

To attain higher quality in analyzing the results of the therapy involving ALA solutions, the measured data were compared with the measurement results of ten conventionally healthy volunteers from the control group (the mean age was 58 ± 11 years). The control group was studied once under the same scheme as the inpatient group but without functional tests or interventions involving the subjects' organisms. The control group's measurements were compared with the measurement data in the group of inpatients before and after the course of treatment with intravenous infusions. The significance of statistical differences between samples was assessed using the Mann–Whitney U test. The probability was considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Since this study is a pilot research aimed at finding possibilities for the application of the LDF method in a portable variant to assess the BMC system's response to the course of intravenous infusions of the solution, as well as due to the limitations to an article's size, this study presents only a comparison between the inpatients' initial parameters before the administration of the therapy and the data measured after ALA course completion.

The patients' measurement results for the main BMC parameters are given in Table 3, showing an insignificant reduction in the index of blood microcirculation and its variability by the end of the treatment course and changes in the blood flow oscillation amplitudes in the active and passive ranges, as well as the opposite changes in the bypass index and nutritive blood flow values. No statistically significant changes have been found in this study in the patient group parameters, however, decreasing or increasing trends in one or another parameter were repeated in almost all patients under study.

Changing trends in the BMC parameters as a result of a therapeutic effect in patients were most apparent in a comparison between their measured values and those of the control group. Figure 2 gives the diagram of differences between the BMC indices in patients before and after the administered therapy and the control group's data on upper (a) and lower (b) limbs.

The data in Fig. 2 show that a decreasing trend in the index of blood microcirculation was observed in patients by the end of treatment with intravenous infusions of ALA in both upper and lower limbs. However, this trend did not reach statistically significant values. The latter result may be explained by different dynamics of interpersonal changes in the parameters of patients. The results of the peripheral blood flow investigations in DM patients in the basal conditions are contradictory [26, 27]. Some studies made similar conclusions on the absence of statistically significant differences between the perfusion parameters in DM patient groups and healthy controls, but the LDF sig-

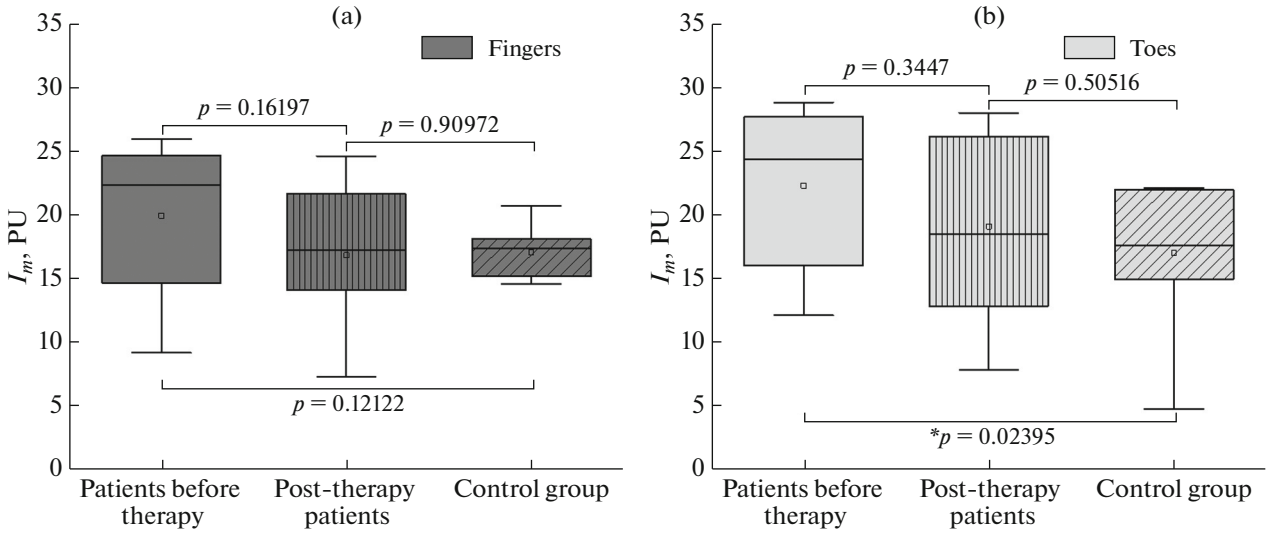

Fig. 2. Comparison between the index of blood microcirculation values before and after the therapy in patients and the control group in upper (a) and lower (b) limbs. (a) Values measured on fingers, (b) on toes, nonhatched boxes, measurements in patients before the start of therapy; vertically hatched boxes, measurements in patients after completing the course of intravenous infusions; diagonal hatched boxes, measurement results in the control group; the central line in the box is the median of the group, and its edges are 25th and 75th procentiles. *, statistical significance of differences was confirmed by the Mann–Whitney test, $p \leq 0.05$.

nal in absolute values was found to be lower in patients [28, 29]. On the contrary, other studies marked considerably higher values in DM patients' microcirculation index [30–32]. The latter authors usually associated the results with the effect of persisting sympathetic neuropathy on the microcirculatory function, which causes an increase in the cutaneous blood flow, especially, in lower limbs [28]. In the light of these observations, a decrease in perfusion in the majority of patients by the end of intravenous infusions may be referred in our case to a positive effect of the administered therapy. This hypothesis is confirmed by the fact that the post-treatment measurement values in patients were brought close to the measurement results shown by the control group, which was shown by the decrease, approaching to statistically insignificant values, in the differences between the samples of patients and the control group (Fig. 2b). These changes are especially significantly expressed in lower and less significantly in upper limbs. This difference may be explained by the predominant involvement of the microvascular bed of lower limbs in the development of diabetic complications, due to their higher susceptibility to different stress factors (more pressure due to wearing shoes and bipedalism, etc.). In general, we should note that different groups of researchers have previously reported in different studies applying the LDF method about functional differences between the microcirculatory bed of upper and lower limbs both in standard conditions and in functional tests [28, 33].

Figure 3 presents a comparison based on measurements obtained with a finger-held (Fig. 3a) and toe-held analyzer (Fig. 3b), between the nutritive blood flow parameter in patients before and after the administered ALA therapy and the control group, as well as a comparison based on measurements on fingers (Fig. 3c) and toes (Fig. 3d) between the shunting index parameter in patients before and after the therapy with ALA and the control group. The given data show a decrease in the nutritive blood flow level with a simultaneous increase in its shunting constituent in patients in the course of treatment. As in the case with the BMC index, after the administered infusions of ALA, the differences between patients and the control group discontinue being statistically significant, i.e., the measured BMC parameters in patients are brought closer to the control values after the administered therapy.

The data of Table 3 and Fig. 3 allow us to conclude that due to the administered therapy, the microcirculatory blood flow in patients is redistributed from nutritive into shunt pathways. These changes may be caused by both a decrease in the index of blood microcirculation in the regions under the study, in total, and a decrease in the metabolic activity of biological tissues (this is confirmed by a decrease in the nutritive blood flow portion), which may be considered as one of the manifestations of a positive effect resulting from the administered therapy. It is also interesting to note a difference in the dynamics of these changes in upper and lower limbs. This difference may be explained by disorders detected by earlier studies devoted to the distribution of microcirculatory blood flow into nutritive and thermoregulatory pathways in a DM patient's foot

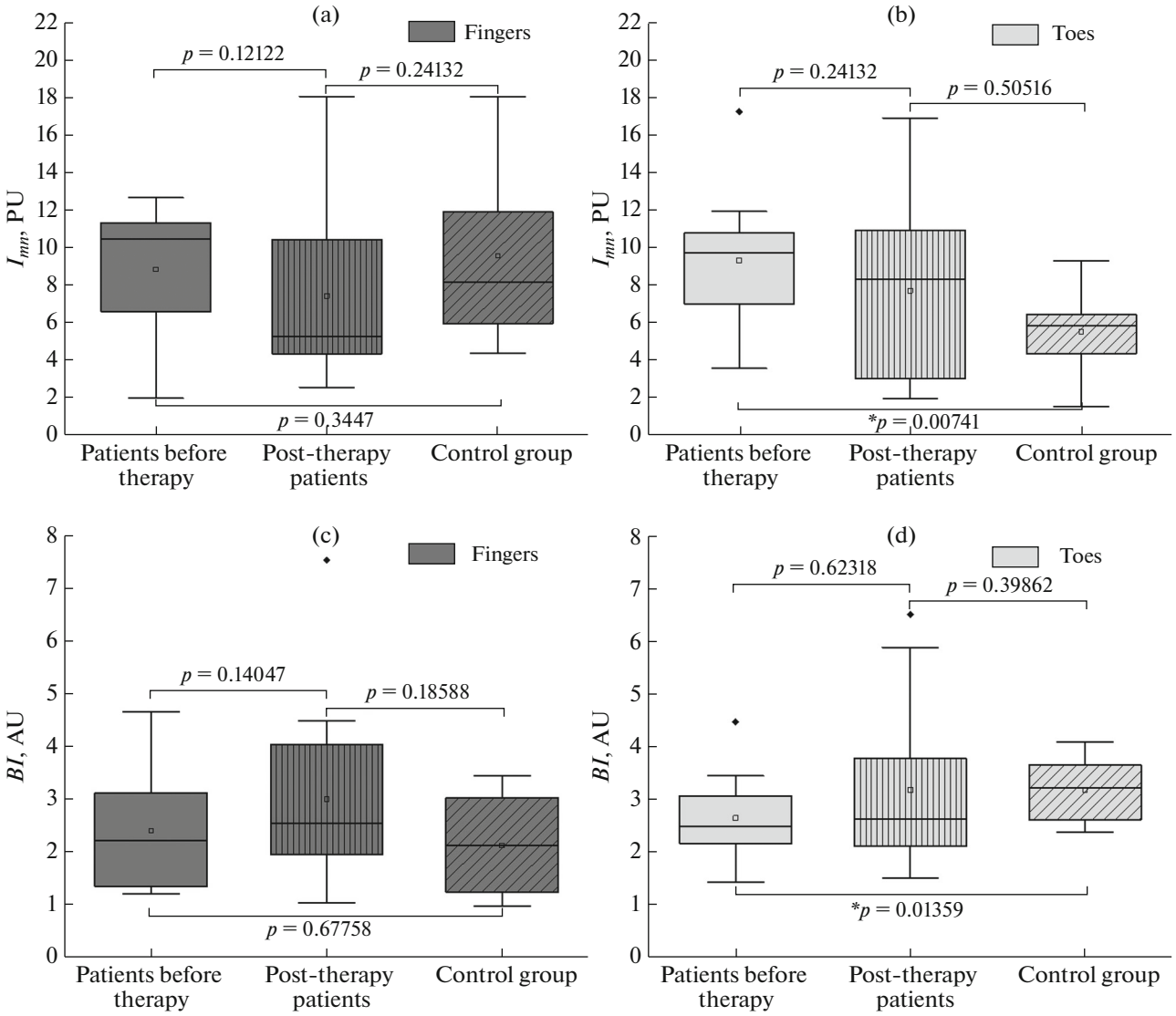

Fig. 3. Changes in the I_{mn} and BI parameters in the course of therapy for upper (a and c) and lower (b and d) limbs. See the designations in Fig. 2.

as a result of a damaging effect of neuropathy on the regulatory function of arteriolo-venular shunts [34].

It is interesting also to note a difference in the dynamics of changes in the normalized active range oscillations in patients' upper and lower limbs (Table 3). The opposite changes in the oscillating LDF signal components in upper and lower limbs may also refer to the above-mentioned disorder in the blood flow distribution into nutritive and shunt pathways, a disorder developing in DM patients exactly in lower limbs, since they are more susceptible to stress factors. A decrease in the amplitudes of oscillations in patients feet in the course of therapy is a sign of a positive ALA effect on the state of microcirculation, since this is the evidence of growth in the oscillating component in the tonus of microvessels, which in the case of a long-duration DM reduces blood supply to microvessels, thus reducing the risks of developing edema and inflammation in tissues.

When comparing the parameters of blood flow oscillations in patients and the control group (Fig. 4), we detected a decrease in the amplitude values of myogenic oscillations in lower limbs of patients at their hospital admission (0.10 ± 0.05 rel. units, AU), compared to the control group (0.12 ± 0.04 AU). This difference did not reach any statistically significant level, but, after the administration of therapy, the parameter values in patients (0.08 ± 0.06 AU) decreased below the control values. This result also confirms the previously suggested hypothesis of a positive effect of the administered therapy on the reduction of metabolic activity in the biological tissues of the region under investigation, since this is the mani-

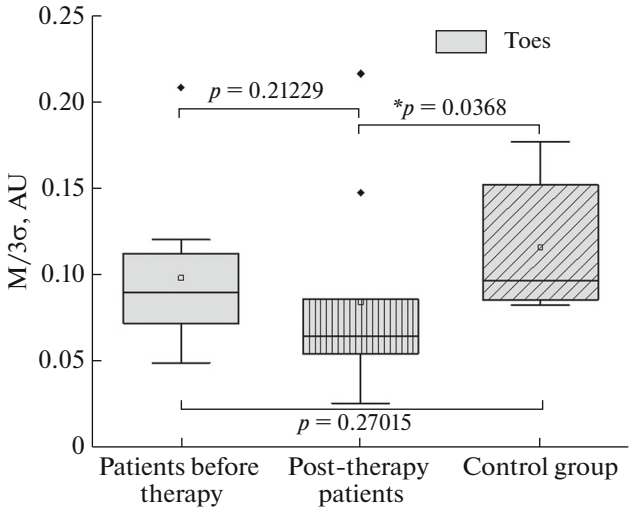

Fig. 4. Changes in the M/3σ parameter during the course of therapy for lower limbs. See the designations in Fig. 2.

festation of elevated tonus in the foot skin precapillary sphincters, their protection from an increased blood supply to capillaries, which in turn contributes to reductions in edema, inflammation, and risks of developing diabetic foot.

Individual studies showed a significant improvement in neuropathy symptoms after a 5-week therapy course based on ALA as a treating agent [35]. We should also note that the treatment involving ALA generates a cumulative effect and may not manifest itself within the first week in terms of microcirculation parameters. The combined therapies with the administration of tableted ALA for several weeks after the course of intravenous infusions are now more popular in medical practice and may give better efficacy [24].

CONCLUSIONS

The increasing prevalence of DM diagnoses and its invalidating complications necessitates the search for new and more efficaceous medication means for managing these complications and more correct efficacy assessments. The application of α-lipoic acid is now recommended as a pathogenetic therapy in DPNs and included in the National Clinical Recommendations for the Treatment of Diabetes Mellitus [36, 37] and the Algorithms of Specialized Medical Care for Diabetes Mellitus Patients [38]. Despite numerous studies confirming the efficacy of ALA for the improvement in the DPN symptoms, its effect on the BMC state, as an important factor in the development of diabetic complications, has not been studied so far in detail.

This integrated and multi-faceted study of changes in the BMC parameters in patients with DM was conducted for the first time during the course of treatment based on intravenous infusions of ALA solution. The distributed system of wireless compact LDF devices was applied to attain this purpose, which allowed us to record the microcirculatory blood flow parameters in four regions of the body directly during the administration of intravenous infusions of ALA.

Changes were detected during the administration of therapeutic agents in the index of blood microcirculation and the distribution of the microcirculatory blood flow into nutritive and shunt pathways, as well as differences in the given changes in upper and lower limbs. When the obtained measurement results were compared with those of the control group, we identified a significant approximation of the measured parameters in patients to the control values as a result of the administered therapy. The detected responses of the BMC system to the therapy with the use of ALA demonstrates a positive effect of this therapy, since these responses are the evidence of a reduction in the blood supply to the microvessels of lower limbs and the evidence of an increase in the tonus of precapillary sphincters in foot skin, which in combination contributes to the prevention of developing edemas and inflammation in tissues, as well as reduces the risk of developing diabetic foot syndrome.

The conducted study shows the possibility and prospects for the application of the LDF method both as a whole and as portable devices of instrumental diagnostics, in particular, in the practice of therapy efficacy assessment in disorders associated with blood microcirculation dysfunctions.

We are planning to confirm the results under this study in further investigations with sizable samples and a more prolonged period of observations. A promising area of focus is the study of a long-term effect of the administration of ALA on the state of BMC in patients after the course of intravenous infusions, which will become the task of further studies.

FUNDING

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INFORMED CONSENT

All study participants gave their written voluntary informed consent signed by them after informing about potential risks and advantages, as well about the nature of forthcoming study.

COMPLIANCE WITH ETHICAL NORMS

All investigations were conducted in full correspondence with the principles of ethics formulated under the 1964 Helsinki Declaration and its subsequent amendments and approved by the Committee on Ethics of the Turgenev Orel State University (meeting protocol no. 15 of February 21, 2019).

CONFLICT OF INTEREST

The authors declare the absence of any apparent and potential conflict of interest related to the publication of this article.

AUTHORS' CONTRIBUTION

E.V. Zharkikh and Yu.I. Loktionova conducted experimental studies, performed data processing, data analysis and interpretation, and prepared the article for publication; V.V. Sidorov and A.I. Krupatkin developed the study concepts and design, performed the obtained data analysis and interpretation, and participated in the approval of the final version of the article for publication; G.I. Masalygina conducted experimental studies, performed the obtained data interpretation, and prepared the publication; A.V. Dunaev developed the study concepts and design, performed the data interpretation, prepared the article for publication, and participated in the approval of the final version of the article for publication.

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