

Laser doppler flowmetry as the advanced non-invasive method of evaluation of microcirculation status in patients with diabetes mellitus



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The World Health Organization defines cardiovascular diseases, chronic respiratory diseases, oncological pathology and diabetes mellitus as the non-infectious diseases of the XXI century [1, 2, 18].

Currently, the problem of DM is one of the most important medical and social challenges worldwide. This is primarily due to the widespread prevalence of the disease and its tendency to further increase in the incidence of diabetes mellitus [1, 11]. Recent data published in the Diabetes Atlas of the International Diabetes Federation (IDF), 10th Edition, 537 million adults are now living with diabetes. If the necessary measures to combat the pandemic are not taken, the estimated 643 million people will suffer from diabetes mellitus by 2030. And by 2045, that number will rise to 784 million [11].

Diabetes mellitus is the most life-threatening with its complications [2]. Diabetic foot syndrome and lower-limb lesions affect 40 to 60 million people with diabetes worldwide [6]. People with diabetes have a risk of amputations that can be by more than 25 times higher than for people without diabetes [10]. However, with comprehensive treatment, a significant proportion of diabetes-related amputations can be prevented.

Therefore, the strategy of the health care system of each country should be directed not only to treatment, but also to early diagnosis and prevention of complications of diabetes in order to maintain public health, improve quality of life and economic development, respectively [7].

Systemic microcirculatory disorders play an important role in the pathogenesis of DM complications [4, 9]. They lead to the development of microangiopathy and neuropathy (through the primary lesion of vessels involved in the blood supply of the peripheral parts of the nervous system). Currently, less than one-third of physicians recognize signs of peripheral neuropathy associated with diabetes. Untimely diagnosis contributes significantly to high morbidity, disability, and mortality [6, 8, 19].

A routine procedure to indirectly evaluate the microcirculation status is the examination of the eye fundus by an ophthalmologist. The method is subjective and reveals microcirculatory changes already after the manifestation of complications, not allowing their early diagnosis, which, eventually, does not allow to fully evaluating microcirculation status in patients for more effective control of the disease [5].

For this purpose, skin, as the most accessible organ, can be an alternative localization to evaluate the state of microcirculatory network [13]. There are many methods to evaluate cutaneous blood flow: videocapillaroscopy, optical coherence tomography, laser Doppler imaging, etc. [15, 17].

The method of laser Doppler flowmetry stands out among other methods by the possibility of non-invasive tests with different types of functional effects, being relatively inexpensive and easy to use, which accounts for high interest [3, 12, 14—17, 20—22].

Objective of the article is to study the experience of the use of laser Doppler flowmetry in clinical practice as a method of studying the state of the microcirculatory bed in patients with diabetes mellitus.

The interest in the study of microvascular system is due to the significant role of capillaries in the basic processes of vital functions of the body, in the trophic support of organs and their direct participation in tissue and cellular respiration [4, 9]. Microcirculation system is one of those important systems, in which various diseases are manifested at the early stages. Human health and life expectancy depend on coordinated work of the heart, major bloodways and microcirculation vessels as a whole [3, 23].

Non-invasive methods have a number of advantages: they are more accessible, with minimal time expenditure, have no contraindications for the investigation, give a clearly expressed result; studies can be widely used in the clinical practice, the obtained indicators can be used in the diagnosis and influence the tactics of treatment, reduce the period of stay in the clinic [13, 15, 17, 21].

In 1972 the method of LDF was first used to evaluate blood microcirculation, when C. Riva et al. measured perfusion of rabbit retina [4]. In medical practice the method was first applied in the 1980s. Thus, in 1982 T. Tenland et al. made serious efforts to adapt the method to measure cutaneous blood microcirculation, and M. Swiontkowski et al. in 1985 applied LDF to evaluate bone marrow perfusion [4].

The principle of LDF operation is to probe the tissue with laser radiation, register the reflected signal and analyze the occurring Doppler frequency shift of radiation scattered by interaction with moving erythrocytes. The analyzed tissue depth is on the average of 1 mm (for the range from green to infrared wavelengths, the thickness of the probed layer can be 0.5 to 2.0 mm) [12]. This layer may contain the following sections of microcirculatory bed depending on tissue type: arterioles, terminal

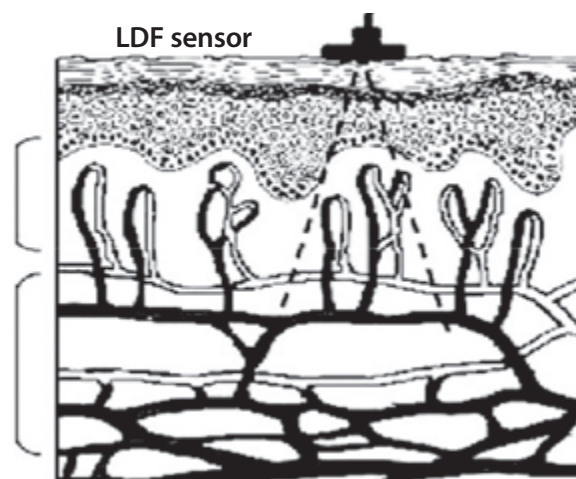


Fig. 1. The scheme of the optic probing of tissue in laser Doppler flowmetry (according to V. I. Makolkin et al., 2001)

arterioles, capillaries, postcapillary venules, venules and arteriolo-venular anastomoses (Fig. 1).

The method allows non-invasive measurement of microcirculation in different localizations: skin, mucous membranes. The analyzed final parameter is called perfusion. It is measured in relative or perfusion units and is directly proportional to the number of erythrocytes and their average velocity. The simplest way to study blood flow using LDF is to record baseline perfusion [20]. Perfusion level is recorded by the device in «real time» mode, and then a graph of perfusion time dependence is formed, called LDF-gram. Routine analysis of LDF-gram consists in calculation of the mean value, standard deviation and variation coefficient of perfusion for a certain period of time [21].

Based on the findings of the LDF evaluation, the type of blood flow is determined, according to which it is possible to establish the presence or absence of endothelial damage and evaluate the effectiveness of the prescribed therapy [7, 14, 19, 23], namely, 1) normotonic; 2) spastic (increased tone of microvessels and decreased blood flow to the microcirculatory system due to spasm of precapillary sphincters); 3) hyperemic (increased blood flow to the microcirculatory system, which is associated with dilatation of microvessels); 4) stagnant-stasis (in paresis of inflow vessels and impaired outflow at the level of capillary and postcapillary section) (Fig. 2).

Along with measurement of the basic level of perfusion, various functional tests are used to study cutaneous blood microcirculation using LDF. They

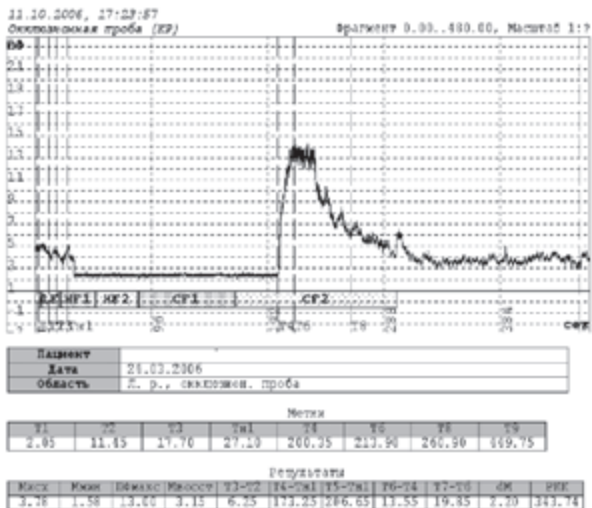


Fig. 2. Normocirculatory type of microcirculation [16]



Fig. 3. Portable laser flowmeter [6]



Fig. 4. Portable laser flowmeter [6]

allow increasing informativeness of the study due to the evaluation of additional involvement of regulatory mechanisms by means of external stimuli. One of the most frequently used functional tests is the occlusion test [12, 14, 21]. The test is aimed at temporary occlusion of blood flow (by pressurizing the sphygmomanometer cuff to suprasystolic values) in the upper or lower limb with subsequent registration of post-occlusive reactive hyperemia. The duration of occlusion can vary from 1 to 5 minutes; the value of the forced pressure varies from 40 mm Hg above systolic to fixed values of 300 mm Hg [14]. Methods of results processing may also vary and investigators analyze maximum, average, and relative values of post-occlusive hyperemia, calculate the area under the graph, etc. [15]. Despite the large number of publications where the above test is applied, it is difficult to compare the results of studies due to the lack of standardization of measurements.

Other frequently used tests are temperature, respiratory and pharmacological ones. Their techniques vary considerably in different investigations [12, 14, 15, 21]. When using pharmacological tests, the measurement results are influenced by the factors determining the efficiency of iontophoresis: the duration of the procedure, the pH of the solution and its concentration, the properties of the solvent, the thickness of the skin, its electrical resistance, the density of sebaceous and sweat glands and the intensity of their activity, as well as a number of other parameters.

The medical market presents contact (Fig. 3—5) and contactless (scanning systems) flowmeters with data transmission to a computer, telephone and corresponding device of a physician.

Mitochondrial stress (oxidative metabolism disorder) is the major mediator of neurodegeneration in DM. High tissue glucose levels result in the accumulation of reduced nicotinamide dihydrogen dinucleotide (NADH) in mitochondria. Imbalance of the redox system (disruption of the NADH to nicotinamide adenine dinucleotide (NAD) ratio), oxidative stress (free radical formation) and mitochondrial stress are also involved in tissue damage in DM. The polyol-sorbitol metabolism pathway is activated by hyperglycemia. Prolonged hyperglycemia is toxic to the macro- and microvascular system; this phenomenon is known as glucose toxicity. The dynamics of energy metabolism coenzymes FAD and NADH and disruption of oxidative

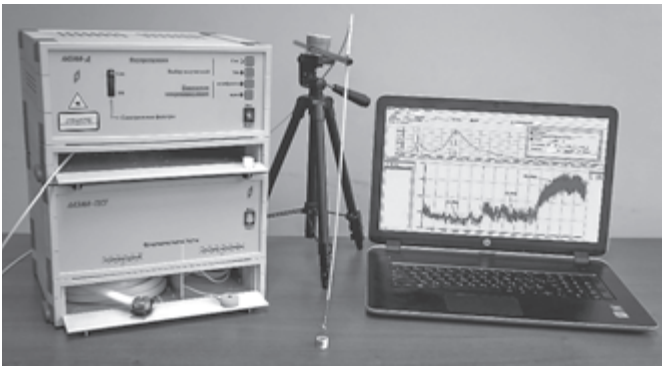


Fig. 5. Laser diagnostic apparatus [6]

metabolism can be studied using laser fluorescence spectroscopy (LFS) [8, 20]. The potential of combined, simultaneous assessment of blood delivery to the microcirculation system by laser Doppler flowmetry and oxidative metabolism by tissue biomarker-coenzymes using LFS method seems undeniable. The combination of these diagnostic methods makes it possible to assess the risk of diabetic foot syndrome [10, 17, 19, 20, 23].

Summarizing the above data, it should be noted that such advantages of LDF as noninvasiveness, the possibility of quantitative assessment of the state of the microcirculatory network, the possibility of using functional tests to determine various regulatory mechanisms made this method one of the most common ways to assess microcirculation (Fig. 6).

A significant part of scientific publications on LDF is related to the study of microcirculation in DM, arterial hypertension, burns, as well as conditions characterized by blood rheology and hemostasis disorders [14, 21]. Nonetheless the abundance of works in this field, the comparison of the findings of

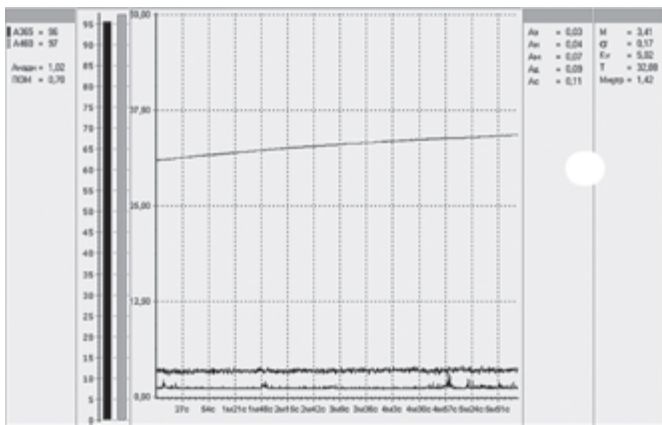


Fig. 6. Research protocol [6]

individual studies, and even more so, the implementation of these results into clinical practice is complicated by a number of metrological and methodological aspects: lack of sample standardization, data recording techniques, design differences in measuring devices, etc. [15, 22].

Among the most promising points of application is the study of microcirculation as part of the early diagnosis of DM and its complications, clarifying the risk of complications, monitoring the effectiveness of treatment [3, 4, 6, 7].

The findings of numerous scientific studies carried out using LDF suggest that the method provides an opportunity to identify microcirculatory changes characteristic of DM patients, such as endothelial dysfunction and nervous regulation of vascular tone in various manifestations. LDF has also demonstrated the ability to identify features of microcirculation in people with early disorders of carbohydrate metabolism and high risk of DM. Perhaps in the future LDF will allow moving from the «purely scientific» use of the method to its practical application in the clinical practice for the diagnosis of disorders in a particular patient.

Most DM patients are not well-informed about the development of DM complications, and therefore this cohort of patients requires constant examination and detection of lesions at the early stage [1, 8, 9].

CONCLUSIONS

1. The possibility of real-time non-invasive quantitative assessment of the state of microcirculatory blood flow and relative ease of use explain the high popularity of LDF in scientific research and make this method promising for use in clinical practice.

2. Unfortunately, the current use of LDF is limited to scientific studies.

3. This method can have important diagnostic value for the study of the state of various levels of microcirculation regulation and is important for dynamic monitoring of the effectiveness of the prescribed treatment.

4. Complex application of LDF and LFS in relation to detection of risk of diabetic foot syndrome will allow personalizing DM therapy.

5. Development of optimal evaluation techniques of microcirculation is a prospect for further research.

Conflict of interest. The author declared no conflicts of interest.

REFERENCES

1. Beaglehole R, Bonita R, Horton R, et al. Priority actions for the noncommunicable disease crisis. *Lancet*. 2011 Apr 23;377(9775):1438-47. doi: 10.1016/S0140-6736(11)60393-0.
2. Bodnar PM, Komissarenko Yul, Mikhalchyshyn GP and others; Endocrinology: A textbook for students. higher honey. textbook institutions. Vinnytsia: New Book, 2020:536.
3. Bychina ES, Panchenkova LA. Functional specifications of microcirculation in patients with arterial hypertension associated with metabolic syndrome and subclinical hypothyroidism. *Medical Visualization*. 2013;(6):100-4 (in Russian).
4. Chernukh AM, Alexandrov PN, Alekseev OV. *Microcirculation*. M.: Medicine;1984. – 432 p.
5. Cohen SR, Gardner TW. Diabetic retinopathy and diabetic macular edema. *Dev. Ophthalmol*. 2016;55: 137-46.
6. Dynnyk OB, Marunchin NA, Mostovyj SE, Endothelial lesions and methods of correction in clinical practice: the role of laser Doppler flowmetry (literature review). *International Journal of Endocrinology*. 2018; 14(8):783-789.
7. Fedorovich AA. Microvascular endothelium and the possibilities of drug-induced correction of microvascular dysfunction. *Lechaschii Vrach*. 2013;(11):77-84 (in Russian).
8. Fernyhough P, McGavock J. Mechanisms of disease: Mitochondrial dysfunction in sensory neuropathy and other complications in diabetes. *Handb Clin Neurol*. 2014;126:353-77.
9. Gutterman DD, Chabowski DS, Kadlec AO, et al. The human microcirculation. Regulation of flow and beyond. *Circ Res*. 2016 Jan 8;118(1):15772. doi:10.1161/CIRCRESAHA.115.305364.
10. Hoffstad O, Mitra N, Walsh J, Margolis DJ. Diabetes, lower-extremity amputation, and death. *Diabetes Care*. 2015;38(10):1852-7.
11. International Diabetes Federation. *IDF Diabetes Atlas*, 10th ed.; 2021.
12. Krupatkin AI, Sidorov VV. Lazernaia dopplerovskaia floumetriia mikrotsirkuliatsii krovi [Laser Doppler flowmeter of blood microcirculation]. Moscow: Meditsina; 2005. P. 3-12 (in Russian).
13. Kubanova AA, Mahakova YuB, Krupatkin AI. Complex noninvasive methods of investigation of the pathophysiological processes in the skin of patients with rosacea. *Vestnik dermatologii i venerologii*. 2015;(59):75-86 (in Russian).
14. Kulikov D, Glazkov A, Dreval A, et al. Approaches to improve the predictive value of laser Doppler flowmetry in detection of microcirculation disorders in diabetes mellitus. *Clin HemorheolMicrocirc*. 2018;70(2):173-9. doi:10.3233/CH-170294 (in Ukrainian).
15. Morozov MV, Gurova OA, Kozlov VI. Laser doppler flowmetry for evaluating skin microcirculation in various parts of the body. *Lazern Med*. 2011;15(2):117-8 (in Russian).
16. Mostovyj SE, Dynnyk OB, Berezovskyj VA. Research of electric activity of myocardium and functional state of microcirculation in ischemic heart disease. *Mistectvo likuvanna*. 2014;(111-112):29-33 (in Ukrainian).
17. Sander SV. Comparative characteristics of laser photoplethysmography and laser doppler flowmetry for testing of foot blood supply. *Clinical Anatomy and Operative Surgery*. 2017;16(2):94-7. doi: 10.24061/1727-0847.16.1.2017.53 (in Ukrainian).
18. Shaienko ZO, Popruga AO, Lihonenko OV. Pathogenesis and clinical course of type 2 diabetes mellitus concomitant with obesity. *World of Medicine and Biology*. 2021;(2):159-62. doc: 10.26724/2079-8334-2021-2-76-159-162.
19. Shapoval SD, Savon IL, Smirnova DA, et al. Peculiarities of the lower extremities perfusion in the patients, suffering complicated syndrome of diabetic foot. *Klinicheskaiia khirurgiia*. 2013;(5):50-4 (in Russian).
20. Shinkin MV, Zvenigorodskaya LA, Mkrtumian AM. Laser Doppler flowmetry and fluorescence spectroscopy as methods for preclinical manifestations of diabetic foot syndrome assessment. *Effective Pharmacotherapy*. 2018;(18):6-12 (in Russian).
21. Sidorov VV, Rybakov YuA, Gukasov VM. Diagnostic approach for assessing the state of the microcirculatory-tissue system using laser technologies and a temperature functional test. *Innovation and Expertise*. 2018;(1):135-41.
22. Vasiliev AP, Streltsova NN. Laser Doppler flowmetry in assessment of specifics of skin microhemocirculation in hypertensive patients and in its comorbidity with 2 type diabetes mellitus. *Russian Journal of Cardiology*. 2015;20(12):20-6 (in Russian).
23. Zheliba MD, Bogachuk MG, Zarezenko TP, Balabuyeva VV, Vovchuk IM. Microcirculation changes in necrotic-inflammatory focus in patients with 2 type diabetes mellitus. *Clinical Anatomy and Operative Surgery*. 2017;16(2):10-11. doi:10.24061/1727-788.

ABSTRACT

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Currently, the problem of diabetes mellitus (DM) is one of the most important medical and social challenges worldwide. This is primarily due to the widespread prevalence of the disease and tendency to further increase in the incidence of diabetes mellitus.

Systemic microcirculatory disorders play an important role in the pathogenesis of DM complications. They lead to the development of microangiopathy and neuropathy through the primary lesion of vessels involved in the blood supply of the peripheral parts of the nervous system. Currently, less than one-third of physicians recognize signs of peripheral neuropathy associated with diabetes. Untimely diagnosis contributes significantly to high morbidity, disability, and mortality.

The author investigates the experience of the use of laser Doppler flowmetry (LDF) in clinical practice as a method of studying the state of the microcirculatory bed in patients with diabetes mellitus.

LDF is a non-invasive quantitative method of microcirculation assessment; its capabilities include the analysis of microcirculatory rhythms and functional testing with different types of provocative effects, which provides with investigating the state of regulatory mechanisms of microcirculation.

The prevention and treatment of various microcirculatory disorders is one of the most important problems of medical practice. The difficulties of studying the microcirculation are caused by the very small size of microvessels and strong ramification of intra-organic vascular networks.

The use of LDF in scientific research will make it possible to reveal the DM-specific changes in microcirculatory bed functioning. The findings of some studies suggest that microcirculatory disorders are not only a pathogenetic link in the development of complications, but they are also observed in patients with early disorders of carbohydrate metabolism and may precede the manifestation of diabetes. However, the method has not yet become widespread in clinical practice.

Keywords: diabetes mellitus, microcirculation, laser doppler flowmetry, spectroscopy, noninvasive diagnostics.

РЕЗЮМЕ

Лазерна доплерівська флоуметрія — сучасний неінвазивний метод оцінки стану мікроциркуляції у хворих на цукровий діабет**З.О. Шаєнко***Полтавський державний медичний університет, Полтава*

Проблема цукрового діабету є однією з найважливіших медико-соціальних проблем сучасності та має глобальний характер, що зумовлено поширенням захворювання і тенденцією до подальшого збільшення кількості хворих на цю недугу.

У патогенезі ускладнень цукрового діабету важливу роль відіграють системні мікроциркуляторні порушення. Вони призводять до розвитку мікроангіопатії та нейропатії (через первинне ураження судин, які беруть участь у кровопостачанні периферичних відділів нервової системи). Менше ніж третина лікарів розпізнають ознаки периферичної невропатії, пов'язаної з діабетом. Несвоєчасна діагностика спричиняє високу захворюваність, інвалідизацію та смертність.

Нами вивчено досвід застосування лазерної доплерівської флоуметрії у клінічній практиці як методу дослідження стану мікроциркуляторного русла у пацієнтів із цукровим діабетом.

Лазерна доплерівська флоуметрія — неінвазивний кількісний метод оцінки мікроциркуляції. Він дає змогу аналізувати мікроциркуляторні ритми і проводити функціональне тестування з різними провокаційними пробами для дослідження стану регуляторних механізмів мікроциркуляції.

Профілактика та лікування різних порушень мікроциркуляції є однією з найважливіших проблем медичної практики. Труднощі вивчення мікроциркуляції зумовлені дуже малим розміром мікросудин.

Використання лазерної доплерівської флоуметрії у наукових дослідженнях дасть змогу виявити характерні для цукрового діабету зміни функціонування мікроциркуляторного русла. Результати деяких досліджень свідчать про те, що порушення мікроциркуляції є не лише патогенетичною ланкою у розвитку ускладнень, а і спостерігаються у пацієнтів з ранніми порушеннями вуглеводного обміну та

можуть передувати маніфестації цукрового діабету. Однак метод ще не набув широкого поширення в клінічній практиці.

Ключові слова: цукровий діабет, мікроциркуляція, лазерна доплерівська флоуметрія, спектроскопія, неінвазивна діагностика.

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