Skin Blood Perfusion and Fluorescence Parameters in Pregnant Women with Type 1 Diabetes Mellitus

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***Abstract*—This work represents the first stage of a study of microcirculation and oxidative metabolism parameters in the skin of women with type 1 diabetes mellitus in early stages of pregnancy. Laser Doppler flowmetry and fluorescence spectroscopy were used to record the diagnostic parameters in the study. The main parameters of LDF recordings of patients under the study (index of microcirculation in the upper and lower extremities, normalised amplitudes of blood flow oscillations), as well as normalised fluorescence values when excited with 365 nm light, were measured and presented.**

Keywords—blood microcirculation, oxidative metabolism, diabetes mellitus, pregnancy, laser doppler flowmetry, fluorescence spectroscopy

I. Introduction

Women with pregestational diabetes mellitus (DM) have an increased risk of adverse pregnancy outcomes for both mother and child. In particular, prior diabetes increases the risks of pre-eclampsia, preterm birth, macrosomia, stillbirth and congenital fetal defects [1]. The urgency of the issue is all the more evident in light of the increasing prevalence of type 1 and type 2 DM in the global population. According to the International Diabetes Federation, there were 463 million people with diabetes worldwide in 2019, and the number is projected to rise to 700 million by 2045 [2].

Adequate glycaemic control and early detection of vascular complications can improve pregnancy outcomes in DM patients and reduce the risk of adverse outcomes [3].

When diagnosing vascular function in pregnancy, it is important first and foremost to consider maternal and fetal safety, so the use of safe and noninvasive diagnostic methods is preferable. The best prospects in this aspect are presented by methods of biophotonics [4, 5]. Endothelial dysfunction seen in the skin of patients with type 1 DM is known to precede the development of target organ microcirculatory disorders. Endothelial function can be assessed non-invasively using laser Doppler flowmetry (LDF).

LDF is a technique for studying blood flow at the level of the microcirculation. By recording the LDF signal, it is possible to obtain information about such diagnostic indicators as the level of tissue perfusion with blood (or index of microcirculation – I_m, measured in perfusion units – p.u.) as well as analyse the influence of different regulatory systems - endothelial, neurogenic, myogenic. By analysing pulse and respiratory waves, it is also possible to obtain information about blood inflow and outflow from the microcirculatory bed. Over its many years of clinical use, it has found wide application in various areas of medicine related to vascular dysfunction. One of the areas of widespread application of this method is also the examination of patients with DM to detect signs of complications before their clinical manifestation [6, 7].

LDF has been used in studies of endothelial dysfunction in diseases of various etiologies, including hypertension [8] and kidney disorders [9]. Endothelial dysfunction has also been investigated using LDF in patients with DM with associated microvascular disorders [10] and without complications [11].

Fluorescence spectroscopy is another optical non-invasive technology that has also found wide application in the clinic of diabetes-related disorders. This technology is used extensively to assess the risk of micro- and macrovascular complications, neuropathy and renal disease in DM.

Several studies have been conducted on the assessment of vascular function in pregnant patients with type 1 DM that have shown that LDF can be used to detect pregnancy abnormalities even before their clinical manifestation [12, 13]. However, the vast majority of studies using LDF to analyse vascular function in patients affected by DM complications during pregnancy have used functional tests, specifically the administration of acetylcholine by ionophoresis. To the best of our knowledge, there have also been no previous studies using non-invasive skin fluorescence measurements alone or together with LDF to assess the risk of diabetic complications in pregnancy. The present work aims to investigate for the first time the basic state of blood microcirculation and oxidative metabolism in pregnant patients with pregestational type 1 DM using LDF and fluorescence spectroscopy.

II. Materials and Methods

Experimental studies were carried out with the participation of 7 patients with pregestational type 1 DM. The average age of the patients was 32, and all were between 7 and 22 weeks gestation. The duration of DM ranged from 17 to 24 years. All patients signed voluntary informed consent to participate in the study and the study protocol was approved by an ethics committee.

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All measurements were taken in the first half of the day immediately after a meal. Recently it was demonstrated that the body position significantly affects the parameters of blood perfusion measured in skin [14]. The patients were seated with their legs stretched forward and their hands resting on their knees (see Fig.1 a). The newly developed wireless wearable LDF and FS monitors "LAZMA-W2" (Aston Medical Technology Ltd., UK; SPE "LAZMA" Ltd, Russia) [15] were used to study microcirculatory blood flow and oxidative metabolic parameters. The analysers were attached to the dorsal surface of the patients' wrists and the inner surface of the upper third of the tibia, the point of greatest girth (the layout of the analysers is shown in the Fig.1 b and c). Four analysers were used simultaneously in the measurements. LDF parameters were measured for 30 minutes, and the autofluorescence spectrum of the skin was also recorded once every minute during the first 10 minutes of the study using 365 nm light.

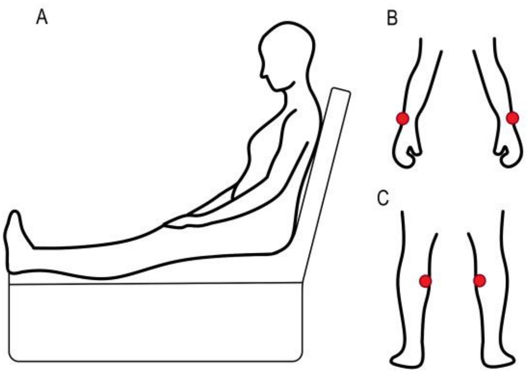

Fig. 1. The position of the volunteers during the experiments (a), the fixation of the monitors on the hands (b) and legs (c) of the volunteers.

Blood pressure, pulse rate and blood glucose were measured before and after each of the measurements. All patients also underwent continuous glucose monitoring with the "Libre Freestyle" system (Abbott, US), which was pre-installed subcutaneously in the forearm area. An installed system measured the values of glucose concentration in the intercellular fluid every 15 minutes for 10-14 days. Glycaemic excursions, their amplitudes and durations, rate of change and standard deviations were assessed from continuous glucose monitoring data.

III. Results

The following microcirculatory blood flow and oxidative metabolic parameters were recorded and analysed as a result of the present study: index of microcirculation (I_m), amplitudes of endothelial (A_e), neurogenic (A_n) and myogenic (A_m) bands, normalised to the standard deviation of the Im, amplitudes of respiratory (A_r) and pulse (A_p) waves, and the skin autofluorescence value when probing with 365 nm light (A_{365}), normalised to backscattered radiation. The values obtained for the upper and lower extremities are shown in the Table. I.

TABLE I. Measured Parameters Of The Studied Patients

Parameter	Values	
	Wrists	*Shins*
I_m, p.u.	4.36±1.21	6.76±1.59
σ, p.u.	0.57±0.23	0.97±0.60
$A_e/3\sigma$, a.u.	0.08±0.02	0.05±0.03
$A_n/3\sigma$, a.u.	0.10±0.02	0.06±0.03
$A_m/3\sigma$, a.u.	0.10±0.02	0.09±0.04
A_r, p.u.	0.13±0.05	0.24±0.07
A_c, p.u.	0.17±0.05	0.30±0.08
A_{365}, a.u.	3.10±1.25	2.39±1.48

The following indices were calculated from continuous glucose monitoring using standard methods [16]: mean glucose level on the day of study ($M_{glucose}$), standard deviation ($\sigma_{glucose}$), the mean amplitude of glycemic excursions (*MAGE*) and the mean of daily differences (*MODD*). The level of $M_{glucose}$ on the day of the study was 6.63 ± 1.71 mmol/l in the study group. The standard deviation $\sigma_{glucose}$ was 2.21 ± 0.71 mmol/l. The *MAGE* and *MODD* indices were 5.37 ± 1.59 and 2.57 ± 1.05 respectively. It should be noted that the mean values of the indices in physiological pregnancy are on average 4.84 for *MAGE* and 0.43 for *MODD*. It can be concluded that the glycaemic excursion is more pronounced in the study group compared to physiological pregnancy.

The LDF data measured at the wrists were also compared with data obtained in a similar way from 7 healthy nonpregnant women with a mean age of 32 years. The comparison results revealed reduced values of myogenic oscillations in the patient group compared to the control group, the data are shown in the Fig.2.

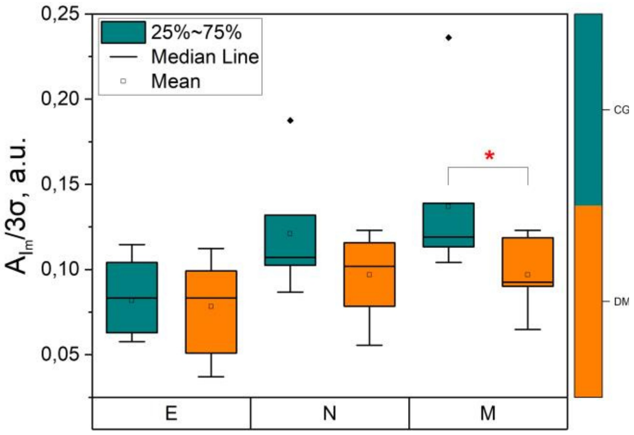

Fig. 2. Comparison of normalised endothelial (E), neurogenic (N) and myogenic (M) oscillation parameters of patients under the study (DM) and controls group (CG).

*- The statistically significant difference between the values was confirmed with $p < 0.05$ using Mann-Whitney test.

The differences found in the microcirculation parameters are of interest for further study. Our results are consistent with previously published data on significantly lower myogenic range oscillations in diabetic patients [17], which may be an early indication of the development of sympathetic autonomic dysfunction as the authors reasoned.

IV. Conclusion

This study is the first to show the combined use of laser Doppler flowmetry and fluorescence spectroscopy together with glucose variability monitoring to assess vascular function and oxidative metabolic status in pregnant patients with previous type 1 DM. The development of this work is seen in the comparison of LDF and FS monitoring data of patients with their glucose variability monitoring data in order to analyse the possible effect of diurnal blood glucose changes on oxidative metabolism and microcirculation.

The combination of continuous glucose monitoring with LDF and fluorescence spectroscopy provides more information on both the parameters of glucose changes and the different behavioural patterns of the blood microcirculatory system and oxidative metabolism as a response to these changes. It is also promising to assess these parameters at different stages of pregnancy and in the postnatal period. This work represents the first step towards studying the impact of pre-existing diabetes on pregnancy complications using biophotonics technology.

REFERENCES

[1] A. Correa, S. M. Gilboa, L. M. Besser, L. D. Botto, C. A. Moore, C. A. Hobbs, M. A. Cleves, T. J. Riehle-Colarusso, D. K. Waller, E. A. Reece et al., "Diabetes mellitus and birth defects," American journal of obstetrics and gynecology, vol. 199, no. 3, pp. 237–e1, 2008.

[2] IDF, "Diabetes atlas. 9th edition," 2019.

[3] F. Dunne, P. Brydon, K. Smith, and H. Gee, "Pregnancy in women with type 2 diabetes: 12 years outcome data 1990–2002," Diabetic Medicine, vol. 20, no. 9, pp. 734–738, 2003.

[4] E. Savchenko and E. Velichko, "The use of speckle correlation analysis to determine blood flow velocity," Optics and Spectroscopy, vol. 128, no. 7, pp. 998–1003, 2020.

[5] N. Ushakov, A. Markvart, D. Kulik, and L. Liokumovich, "Comparison of pulse wave signal monitoring techniques with different fiber-optic interferometric sensing elements," in Photonics, vol. 8, no. 5. Multidisciplinary Digital Publishing Institute, 2021, p. 142.

[6] E. Zharkikh, V. Dremin, E. Zherebtsov, A. Dunaev, and I. Meglinski, "Biophotonics methods for functional monitoring of complications of diabetes mellitus," Journal of Biophotonics, vol. 13, no. 10, p. e202000203, 2020.

[7] I. Kozlov, E. Zherebtsov, G. Masalygina, K. Podmasteryev, and A. Dunaev, "Laser doppler spectrum analysis based on calculation of cumulative sums detects changes in skin capillary blood flow in type 2 diabetes melitus," Diagnostics, vol. 11, no. 2, p. 267, 2021.

[8] K. Farkas, E. Kolossvary, Z. J ´ arai, J. Nemcsik, and C. Farsang, "Non-invasive assessment of microvascular endothelial function by laser doppler flowmetry in patients with essential hypertension," Atherosclerosis, vol. 173, no. 1, pp. 97–102, 2004.

[9] A. Kruger, J. Stewart, R. Sahityani, E. O'riordan, C. Thompson, S. Adler, R. Garrick, P. Vallance, and M. Goligorsky, "Laser doppler flowmetry detection of endothelial dysfunction in end-stage renal disease patients: correlation with cardiovascular risk," Kidney international, vol. 70, no. 1, pp. 157–164, 2006.

[10] J. Škrha, M. Prázný, T. Haas, J. Kvasnička, and B. Kalvodová, "Comparison of laser-doppler flowmetry with biochemical indicators of endothelial dysfunction related to early microangiopathy in type 1 diabetic patients," Journal of Diabetes and its Complications, vol. 15, no. 5, pp. 234–240, 2001.

[11] M. B. Gomes, A. S. Matheus, and E. Tibiriçá, "Evaluation of microvascular endothelial function in patients with type 1 diabetes using laserdoppler perfusion monitoring: which method to choose?" Microvascular research, vol. 76, no. 2, pp. 132–133, 2008.

[12] J. E. Ramsay, R. J. Simms, W. R. Ferrell, L. Crawford, I. A. Greer, M.-A. Lumsden, and N. Sattar, "Enhancement of endothelial function by pregnancy: inadequate response in women with type 1 diabetes," Diabetes Care, vol. 26, no. 2, pp. 475–479, 2003.

[13] F. Khan, J. J. Belch, M. MacLeod, and G. Mires, "Changes in endothelial function precede the clinical disease in women in whom preeclampsia develops," Hypertension, vol. 46, no. 5, pp. 1123–1128, 2005.

[14] A. A. Fedorovich, Y. I. Loktionova, E. V. Zharkikh, M. A. Mikhailova, J. A. Popova, A. V. Suvorov, and E. A. Zherebtsov, "Body position affects capillary blood flow regulation measured with wearable blood flow sensors," Diagnostics, vol. 11, no. 3, p. 436, 2021.

[15] E. A. Zherebtsov, E. V. Zharkikh, I. Kozlov, A. I. Zherebtsova, Y. I. Loktionova, N. B. Chichkov, I. E. Rafailov, V. V. Sidorov, S. G. Sokolovski, A. V. Dunaev et al., "Novel wearable vcsel-based sensors for multipoint measurements of blood perfusion," Proc. SPIE, vol. 10877, p. 1087708, 2019.

[16] S. E. Siegelaar, F. Holleman, J. B. Hoekstra, and J. H. DeVries, "Glucose variability; does it matter?" Endocrine reviews, vol. 31, no. 2, pp. 171–182, 2010.

[17] V. Urbancic-Rovan, A. Stefanovska, A. Bernjak, K. Azman-Juvan, and A. Kocijančič, "Skin blood flow in the upper and lower extremities of diabetic patients with and without autonomic neuropathy," Journal of vascular research, vol. 41, no. 6, pp. 535–545, 2004.