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MARKERS OF ENDOTHELIAL DYSFUNCTION AS PREDICTORS OF THE DIABETIC RETINOPATHY TREATMENT IN TYPE 2 DIABETES MELLITUS

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Resume. We developed a prognostic model for assessing the effectiveness of diabetic retinopathy (DR) treatment in type 2 diabetes mellitus (T2DM) based on the determination of endothelial dysfunction markers. For the first time, a model for predicting the effectiveness of DR treatment using markers of endothelial dysfunction was built for the Ukrainian population, which included EMAP-II and eNOS, indicating the key importance of these markers for determining the effectiveness of DR treatment.

Keywords: type 2 diabetes, diabetic retinopathy, prognosis, modeling, endothelial dysfunction, EMAP-II, endothelial NO-synthasession.

Background. Modern treatment of diabetes mellitus (DM) is based on strict glycemic control with the use of insulin therapy, as well as individually-oriented selection of drugs to lower glucose levels [1]. Constant monitoring and a flexible approach to updating treatment tactics in accordance with modern scientific achievements are of paramount importance. The treatment of diabetic retinopathy (DR) is no exception, which has changed significantly over the past two decades due to the introduction of new technologies, including intravitreal injections of anti-VEGF drugs

and steroids, as well as laser therapy [2]. Because the needs of patients in certain groups may differ, treatment of DR should be personalized. Glycemic and blood pressure control can slow the progression of DR in the early stages, and in the late stages, laser treatment and/or anti-VEGF therapy can reduce vision loss [3]. The current treatment strategy for DR is based on a combination of anti-VEGF therapy, laser coagulation, and surgical interventions, depending on the clinical case, with optimal control of systemic risk factors. On the other hand, despite the widespread implementation of modern technologies, complications and relapses are possible after these interventions in the short and long term [4]. Today, it is well-founded that one of the leading mechanisms of the onset and further progression of DR is endothelial dysfunction with damage to the vascular wall and a decrease in the protective effects of nitric oxide (NO) [5]. Metabolic disorders and accumulation of reactive oxygen species (ROS) inhibit endothelial NO synthase (eNOS), which inhibits endothelium-mediated vasodilation [6]. Another consequence is the initiation of sluggish metabolic inflammation, the markers of which are high-sensitivity C-reactive protein (hs-CRP) and pro-inflammatory cytokines, which have a positive correlation with the severity of DR [7]. Endothelial damage in DR reflects an increase in the formation of endothelin 1 (ET-1) in the vascular wall [8]. Another marker of endothelial dysfunction is endothelial monocyte-activating polypeptide-II (EMAP-II), which has proinflammatory and antiangiogenic activities.

The **aim** of the study is to develop a prognostic model for assessing the effectiveness of diabetic retinopathy (DR) treatment in type 2 diabetes mellitus (T2DM) based on the determination of endothelial dysfunction markers.

Material and methods. 136 patients (136 eyes) with T2DM and DR were examined, who were divided into groups: 1st – with non-proliferative DR (60 eyes), 2nd – with preproliferative DR (PPDR; 42 eyes) and 3rd – with proliferative DR (PDR; 34 eyes). Patients were examined using ophthalmological methods; In serum, high-sensitivity C-reactive protein (hs-CRP), endothelin-1, endothelial monocyte-activating polypeptide-II (EMAP-II), endothelial NO-synthase (eNOS), interleukins (IL-1β and IL-6) were determined by enzyme-linked immunosorbent assay. The content of nitric oxide metabolites (NOx) in the blood was determined by biochemical methods. Repeated ophthalmological examination was performed after 2 years of treatment, which included conservative, laser photocoagulation, anti-VEGF, surgical (vitrectomy) and their combination. Analysis of the study results was performed in the EZR v.1.54 package (Austria).

Results. In T2DM patients with various stages of DR, a gradual increase in the blood content of all endothelial dysfunction markers was found compared to controls (1.9-16.4 times; $p<0.001$). The exception was eNOS, the content of which gradually decreased (by 1.5-3.7 times; $p<0.001$). All indicators (except NOx) were associated with the risk of rapid progression of DR (AUC=0.77-0.88). The maximum AUC values (>0.8) were observed in models with EMAP-II, hc-CRP and IL-6. The specificity of models with hc-CRP, EMAP-II, eNOS and IL-6 exceeded 85%, but their sensitivity was quite low (from 51.9% to 81.0%), which limited their use in practical studies. The

multifactorial model for risk predicting of rapid DR progression included EMAP-II and eNOS, which indicated the key importance of these markers for determining of DR treatment effectiveness. The model had excellent quality indicators AUC=0.92 (95% CI 0.86-0.96; sensitivity – 81.0%, specificity – 91.2%) and excellent quality for all treatments (AUC was from 0.85 to 1.0).

The close relationship between endothelial dysfunction indicators and progression of DR and the results of its treatment during 2 years of observation showed the fundamental possibility of their use as biomarkers. Thus, we found a progressive increase in the blood content of hc-CRP in patients with DR, which was consistent with the data of a large meta-analysis [9]. It was also found that hc-CRP is able to predict microvascular complications in patients with type 2 diabetes and has direct links with pro-inflammatory and angiogenic factors [10].

The results of our study, among all the markers of endothelial dysfunction, focus on EMAP-II and eNOS. It has been shown that there is a direct relationship between EMAP-II and indicators of carbohydrate and lipid metabolism in diabetes, and EMAP-II levels in serum reflect the presence of microvascular complications [11]. Our isolation of this indicator through mathematical modeling indicated an independent effect of EMAP-II on the progression of DR and proved its ability to be considered as an independent biomarker of DR progression.

The results obtained confirmed the importance of depletion of eNOS, which is expressed in endothelial cells, provides physiological vasodilation, controls vascular tone and blood pressure, and has a vasoprotective and anti-atherosclerotic effect [12]. Under conditions of chronic hyperglycemia, excess NO, produced by inducible NOS under the influence of inflammatory mediators, interacts with reactive oxygen species to form highly toxic peroxynitrite, which causes apoptosis of retinal cells [6]. Impaired eNOS activity leads to a decrease in NO bioavailability, increased oxidative stress, and endothelial dysfunction, which is considered one of the mechanisms of microvascular damage in DR [13].

Thus, we showed that most of the studied predictors of endothelial dysfunction were associated with treatment outcomes, which at the evidential level proved their important role in the pathogenetic mechanisms of DR. However, the low sensitivity of the obtained models limited their use in clinical practice. In order to optimize the prognosis, a multivariate analysis was used, which revealed 2 main biomarkers – the content of EMAP-II and eNOS in the blood, which could be used to predict with high accuracy the adverse outcome of all applied treatment methods. Thus, for the first time for the Ukrainian population, a model for predicting the effectiveness of DR treatment using endothelial dysfunction markers was built.

Conclusion. Thus, markers of endothelial dysfunction were associated with the results of DR treatment. For the first time, a model for predicting the effectiveness of DR treatment has been built for the Ukrainian population, highlighting the most significant markers of endothelial dysfunction – EMAP-II and eNOS.

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THE CONTENT OF NEURON-SPECIFIC ENOLASE IN AQUEOUS HUMOR MAY BE A PREDICTOR OF DIABETIC RETINOPATHY IN TYPE 2 DIABETES

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Resume. The study investigated the potential value of measuring neuron-specific enolase (NSE) as a marker of neuronal-glial damage in diabetic retinopathy. Its local measurement in intraocular fluid (IOP) may reflect the severity gradient of diabetic retinopathy (DR) and enhance risk stratification.

Keywords: diabetic retinopathy; type 2 diabetes; neuron-specific enolase; biomarkers; IOP; disease progression.

Background. Diabetic retinopathy (DR) is one of the leading causes of blindness and moderate/severe visual impairment worldwide [1]. According to the GBD/VLEG consortium, in 2020 it accounted for a significant share of vision loss among people ≥50 years of age, which has been increasing over the past 30 years [1]. Against the background of the global epidemic of diabetes mellitus (DM) (≈537 million patients as of 2021 with a prospect of ≈783 million by 2045 [2]), the number of patients at risk of DR is expected to continue to increase. This highlights the need for better risk stratification and personalized care for such patients.

Neuron-specific enolase (NSE) is a marker of neuronal-glial injury. Its local measurement in aqueous humor (AH) may reflect the severity gradient of diabetic retinopathy (DR) and enhance risk stratification. In ophthalmology, increased NSE has been described in retinal detachment (serologically and in intraocular media) [3], as well as in retinoblastoma, where NSE levels in the intraocular fluid (IOL) and vitreous humor reach high concentrations and are of diagnostic significance [4, 5]. Regarding diabetic pathology, systemic studies have shown increased serum NSE in patients with