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ENDOTHELIN-1 CONTENT IN BLOOD AS A POSSIBLE BIOMARKER OF DIABETIC RETINOPATHY

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Abstract. *In a cohort of patients (136 people) with type 2 diabetes mellitus and diabetic retinopathy, an increase in the content of endothelin-1 in the blood serum was found, which allowed to determine its borderline levels at different stages of DR and predict its course after 2 years of observation.*

Keywords: *type 2 diabetes, diabetic retinopathy, prognosis, modeling, endothelin-1, biomarkers.*

Endothelin-1 (ET-1) is a 21-amino acid hormone synthesized by the endothelium and helps maintain basal vascular tone and metabolic function under normal conditions, and in hyperglycemia causes vasoconstriction, affects the plasma lipid profile and insulin signaling, causing the connection between insulin resistance, obesity and microvascular complications [1]. ET-1 is the most abundant member of the endothelin protein family (ET-1, ET-2 and ET-3). It has a potent vasoconstrictor effect and is synthesized mainly by damaged endothelium with proliferative, profibrotic and pro-inflammatory properties [2].

Decreased nitric oxide production and increased ET-1 production in the vascular wall may contribute to oxidative stress and chronic metabolic inflammation with the development of endothelial dysfunction and increased vasoconstrictor activity [3]. Increased ET-1 production contributes to arterial aging and the development of atherosclerotic changes, which are associated with increased arterial stiffness. In addition, it participates in the complex regulation of blood pressure through synergistic interaction with angiotensin II, regulates catecholamine production and sympathetic activity, affects renal hemodynamics and water-salt balance, and regulates baroreceptor activity and myocardial contractility [3]. Increased plasma ET-1 levels have been demonstrated in diabetes mellitus [2]. It was also significantly higher in patients with diabetic retinopathy (DR) than in the control group without diabetes and was positively correlated with the resistance index and negatively

correlated with the peak systolic and diastolic volumes of the central retinal artery (fluorescence angiography data) [4]. Thus, an increase in the content of ET-1 in the blood plasma corresponds to disturbances in ocular hemodynamics and may play an important role in the early diagnosis of DR.

Aim: to determine the endothelin-1 blood content at different stages of diabetic retinopathy and the possibility of its use as a diagnostic and prognostic factor of its progression.

Materials and methods. The study design was cohort, prospective and randomized. 136 patients with type 2 diabetes and DR were examined, in which the indicators of the worst eye in terms of DR were taken into account. Patients were divided into groups according to the stage of DR: 1st – with non-proliferative DR (NPDR; 60 eyes), 2nd – with preproliferative DR (PPDR; 42 eyes) and 3rd – with proliferative DR (PDR; 34 eyes). During 2 years of observation, patients were treated with different methods: conservative, anti-VEGF therapy, surgical and combined. Absence of progression of DR was determined when ophthalmological indicators were stable, slow progression was determined when some indicators worsened, while rapid progression was determined when the next stage of DR was established and/or most indicators significantly worsened (for patients with PDR). The content of endothelin-1 was determined in serum by enzyme-linked immunosorbent assay. Analysis of the study results was performed in the EZR v.1.54 package (graphical interface to R statistical software v.4.0.3, R Foundation for Statistical Computing, Austria).

Results. The ET-1 blood content in patients with different stages of DR significantly increased compared to the control group. Thus, in patients with NPDR it was 2.2 times higher than the control level, in PPDR – 3.8 times, in PDDR – 4.1 times ($p<0.001$ for all comparisons). At the same time, the content of ET-1 in patients with PPDR and PDDR did not differ statistically significantly ($p>0.05$), but was higher than that in patients with NPDR (1.7-1.9 times; $p<0.05$). Thus, during the development of DR, ET-1 had two growth steps – the first in NPDR and the second – with the progression of retinopathy to the PPDR/PDR stages.

The results obtained substantiated the possibility of using the content of ET-1 as a diagnostic biomarker of DR. To calculate the optimal classification thresholds, the One-vs-All method [5] was used, which distinguished 3 classes according to the study groups. The optimal threshold for each class was chosen according to the Youden Index: for the 1st class (control) it was 0 pg/ml, for the 2nd (NPDR) – 1.015 pg/ml and for the 3rd (PPDR/PDR) – 2.0 pg/ml. The overall prediction accuracy was 92.5% (95% CI 87.4-95.7%).

The calculations given allowed us to determine the cut-off levels of ET-1 at different stages of DR. Values less than 1.015 pg/ml were characteristic of the control group. With an ET-1 content of 1.016 pg/ml to 2.0 pg/ml, patients had NPDR (sensitivity – 90%, specificity – 90%). The ET-1 content of more than 2.0 pg/ml was characteristic of patients with PPDR and PDR (sensitivity – 97.2%, specificity – 92.1%).

At the next stage of the study, the task was set to clarify the relationship between ET-1 and the progression of DR during 2 years of observation. In our previous study on a large cohort of patients (358 eyes), it was shown that rapid progression after 2 years of observation was observed in 41.6%, and the remaining patients had slow progression or no progression [6]. To solve this problem, the method of constructing logistic regression models was used. The outcome variable Y=0 for patients who achieved no progression or slow progression of DR after 2 years (57 patients), variable Y=1 for patients who experienced rapid disease progression (79 patients).

The risk of DR progression increased 5.2-fold for every 1 pg/ml increase in blood ET-1 ($p<0.001$; OR=5.18; 95% CI 2.69-9.98). The area under the operating characteristic curve of the prediction AUC=0.77 (95% CI 0.61-0.84), indicating a strong association between ET-1 content and DR progression. The sensitivity of the model was 81.0% (95% CI 73.5%-90.4%), and the specificity was 64.9% (95% CI 57.7%-78.6%).

Conclusion.

Thus, the study established the diagnostic and prognostic value of ET-1 blood levels and showed its important role in the occurrence and progression of NPDR. The

cut-off ranges of ET-1 levels for different stages of DR were established, which had a fairly high predictive accuracy (92.5%), as well as the risk of DR progression within 2 years based on ET-1 levels.

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