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MicroRNA-146A-5p IN DIFFERENT STAGES OF DIABETIC RETINOPATHY

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Resume. The expression of microRNA-146a-5p in a cohort of patients with type 2 diabetes clearly corresponded to the stages of diabetic retinopathy. In addition, its diagnostic and prognostic significance as a marker of type 2 diabetes, diabetic retinopathy and its severe stages in patients from the Ukrainian population was shown.

Keywords: Diabetic Retinopathy; Diabetes Mellitus, Type 2; MicroRNAs; MicroRNA-146a; Gene Expression Regulation; Biomarkers; Disease Progression.

Background. MicroRNAs (miRs) are a class of evolutionarily conserved short non-coding RNAs, containing about 19-22 nucleotides, that regulate the expression of messenger RNA [1]. By participating in the regulation of mRNA target expression, miRs play important roles in a wide variety of biological systems and processes, such as cell differentiation, proliferation, apoptosis, and metabolism, making them promising

clinical biomarkers [2]. MiR-146a is one of the most studied miRNAs due to its central role in immune homeostasis and the control of innate and adaptive immune responses [3]. Based on existing data, it qualifies as an ideal biomarker for the diagnosis, prognosis, and assessment of the activity of immune and non-immune inflammatory disorders. Among the "anti-inflammatory" miRNAs, miR-146a is distinguished as a negative regulator of NF-κB, which is often downregulated in diabetic retinopathy (DR). It has been established that miR-146a-5p is a key negative regulator of inflammatory processes [4]. In particular, NF-κB induces the expression of miR-146a-5p, which, in turn, suppresses target genes important for NF-κB activation (feedback loop) [4]. In the large EURODIAB study in patients with type 1 diabetes, higher levels of miR-146a-5p were associated with reduced odds of DR (OR≈0.4 after adjustments), which is consistent with its anti-inflammatory effects [5]. Studying new predictors of the DR development and progression in diabetes 2 type (DM), in particular the expression of microRNAs, is a relevant issue in modern clinical ophthalmology.

Aim. To establish the diagnostic and prognostic significance of microRNA-146a-5p in the diabetic retinopathy progression in patients with type 2 diabetes.

Materials and methods. The study included 68 patients (68 eyes) with diabetes 2 type, 30 men (44%), 38 women (56%). The patients' age was 60.6±7.1 years, and the duration of diabetes was 6.3±5.3 years. The control group included 12 people (12 eyes) who did not have diabetes (DM0). Group 1 included 15 patients who had type 2 diabetes but no signs of DR were detected (DR0), group 2 included 15 patients with nonproliferative DR (NPDR), group 3 included 14 patients with preproliferative DR (PPDR), and group 4 included 12 patients with proliferative DR (PDR). The relative expression of miRNA-146a-5p was determined by real-time polymerase chain reaction (Thermo Fisher Scientific; USA). For statistical analysis, the EZR v.1.54 package (Austria) was used.

Results and Discussion. In patients with type 2 diabetes who did not have DR, the expression of miRNA-146a-5p was significantly reduced by 1.2 times compared to controls (DM0), in patients with NPDR – by 1.6 times, in patients with PPDR – by 2.9 times, and in patients with PDD – by 4.2 times ($p<0.05$). In pairwise comparisons of all groups, all differences were statistically significant, with the exception of PPDR vs PDD ($p=0.10$). Spearman correlation analysis showed a strong inverse relationship between miRNA-146a-5p and the duration of diabetes ($\rho=-0.91$; $p<0.0001$). Logistic regression analysis showed that decreased expression of miRNA-146a-5p was an independent predictor of the development of DR ($p=0.005$). Classification thresholds were established for the expression of miRNA-146a-5p: for diabetes it was 1.26 standard units; for – 0.95 standard units; for severe stages of DR (PPDR and PDR) – 0.71 standard units.

A review of current medical research has found reduced levels of miR-146a in the blood of patients with type 2 diabetes [6]. Dysregulation of miR-146a expression has been associated with progression of nephropathy, neuropathy, wound healing, olfactory dysfunction, cardiovascular disorders, and retinopathy in patients with diabetes.

Clinically, higher circulating levels of miR-146a have been associated with a lower risk of DR in type 1 diabetes, and genetic variants of the rs2910164 gene of the miR-146a gene affect early ocular neurodegenerative markers [5]. miR-146a-5p levels were significantly lower in patients with DM compared with controls (p=0.039). Logistic regression analysis showed that miR-146a-5p levels were inversely associated with a reduced risk of diabetic complications (OR 0.34; 95% CI 0.14-0.76), especially with DM (OR 0.40; 95% CI 0.16-0.99), regardless of age, sex, diabetes duration, glycated hemoglobin, arterial hypertension, and other factors [5].

The cited data are consistent with our results. The expression of miR-146a-5p in the cohort of patients with type 2 diabetes according to the results of our study clearly corresponded to the stages of DR. In addition, we have shown for the first time its diagnostic and prognostic significance as a marker of type 2 diabetes, DR and its severe stages in patients from the Ukrainian population.

Conclusion. For the first time, in patients with type 2 diabetes from the Ukrainian population, the diagnostic and prognostic significance of the miRNA-146a-5p expression level as a biomarker of the DR development and progression has been shown.

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