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PROGRESSION OF DIABETIC NON-PROLIFERATIVE RETINOPATHY IN TYPE 2 DIABETES MELLITUS: THE CONNECTION WITH THE BLOOD ENDOTHELIAL MONOCYTE-ACTIVATING POLYPEPTIDE-II LEVEL

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Relevance. The numerous pro-inflammatory and antiangiogenic properties of endothelial monocyte-activating polypeptide-II (EMAP-II) suggest its possible role in the onset and progression of diabetic non-proliferative retinopathy (DNPR) in type 2 diabetes mellitus (T2DM).

Objective – is to determine the blood EMAP-II in the DM2 patients and to establish its connection with the progression of DNPR.

Material and methods. We examined 91 patients with DM2 (182 eyes), who were divided into groups: 1st – there was no DNPR in both eyes and 2nd – there were no retinopathy in one eye, and isolated vascular anomalies were noted in the other (ETDRS level 14, 15). The control group included 25 patients of the corresponding age and gender. The patients were re-examined after 1 year. The level of EMAP-II was determined by the enzyme immunoassay in blood plasma once at the beginning of the study. Statistical packages MedStat and MedCalc v.15.1 (MedCalc Software bvba) were used for statistical research.

Results. The analysis of clinical and laboratory parameters showed that the initial manifestations of diabetic retinal lesions were manifested in 27.5% of patients after 7.16 ± 1.11 years and were accompanied by greater glycemia. The level of EMAP-II in DM2 was many times higher than in the control, which depended on the presence of diabetic vascular changes in the retina: in patients without changes in the retina (group 1) – by 3.7 times, and in patients with initial vascular anomalies (group 2) – 5.2 times ($p < 0.001$). The level of EMAP-II at the beginning of the study was associated with the progression of diabetic changes in the retina after 1 year – with their presence, it was 1.5 times higher than without them ($p < 0.001$). Stratification by stage of DNPR after 1 year also showed the dependence of the severity of diabetic changes in the retina on the initial level of EMAP-II: in the presence of single vascular anomalies and initial DNPR, it was increased by 3-4 times, while with moderate DNPR – 5.9 times ($p < 0.001$ for all comparisons).

Conclusion. Thus, a significant increase in the level of EMAP-II in T2DM was established and the dependence of the initial diabetic changes in the retina and the degree of their progression in 1 year after the increasing of the blood EMAP-II level.

Key words: diabetic nonproliferative retinopathy, type 2 diabetes mellitus, EMAP-II.

Relevance. The current state of the epidemiology of type 2 diabetes mellitus (DM2) is characterized by a progressive increase in morbidity along with a high rate of disability [1]. The number of patients in the world has more than quadrupled in the last 40 years [2, 3]. According to the International Diabetes Federation (IDF), the incidence forecast for 2045 will be 629 million people [4]. In 2017, 1.27 million patients were registered in Ukraine, and in 2019 – 1.5 million [5]. At the same time, almost 94 million people in the world have eye damage caused by diabetes [6].

DM2 is considered as a disorder of carbohydrate metabolism, the basis of which is tissue insensitivity to insulin (insulin resistance) on the background of chronic hyperglycemia [3, 4]. The latter is the main pathogenic factor in the development of micro- and macrovascular complications [7, 8]. The most common and early complication of DM2 is retinal vascular microangiopathy

– diabetic retinopathy [9, 10]. This level is determined by a modified ETDRS scale in the system of clinical signs Airlie House [11]. In DNPR, the following signs are present in the retina: microaneurysms (MA) and microhemorrhages (MH), intraretinal microvascular abnormalities (IRMA), retinal venous abnormalities, and retinal nonperfusion. Their main causes are damage of the capillary endothelium with increased permeability and apoptosis, loss of pericytes, chronic inflammation [8, 9].

Over the last three decades, some attention has been paid to endothelial monocyte activating polypeptide-II (EMAP-II), which is a proinflammatory cytokine and chemoattractant for monocytes and granulocytes with potent antiangiogenic properties [12, 13]. Its precursor, proEMAP is identical to the p43 component of the tRNA multisynthetase complex and involved in protein translation. ProEMAP/p43 and EMAP-II act at many

levels and on many cell types, including endothelial cells, immune cells and fibroblasts.

EMAP-II has the ability to inhibit primary and metastatic tumor growth due to its potent effect on endothelial cells (by activating their apoptosis), reduces the expression of the main inducer of angiogenesis – vascular endothelial growth factor (VEGF) [14], inhibits the effects of hypoxia-inducible factor (HIF-1 α) [15] and enhances the action of tumor necrosis factor (TNF α) [16]. EMAP-II binds to the α 5 β 1-integrin receptor on the cell surface, leading to its internalization into the cytoplasm, where it interacts with its cytoplasmic partner PSMA7, a component of the proteasome degradation pathway. This interaction increases the degradation of HIF-1 α , even under conditions of hypoxia, which inhibits its numerous proangiogenic effects [15].

The role of EMAP-II in initiating and maintaining the inflammatory response is extremely important – it is locally expressed near the site of injury, marking it as a «find me» signal for the recruitment of macrophages and neutrophils [12]. EMAP-II-mediated changes in macrophages which are induced mainly by signal transducer and transcription activator-3 (STAT3) and Janus-associated kinase (JAK) [17]. Inhibition of JAK1/2 and/or knockdown of STAT3 cancel the gene set, which is activated by EMAP-II. Activation of STAT3, mediated by EMAP-II, coincides with changes in the expression of pro- and anti-inflammatory genes in macrophages.

Thus, the complex of pro-inflammatory and anti-angiogenic properties of EMAP-II suggest its possible role in the occurrence and progression of initial vascular diabetic changes in DNPR.

Aim: to determine the blood EMAP-II level in the DM2 patients and to establish its connection with the progression of DNPR.

MATERIAL AND METHODS

We examined 91 patients (182 eyes) with DM2, aged 42 to 80 years, who were examined and treated on the basis of the Municipal Enterprise «Consultative and Diagnostic Center» Sviatoshyno district of Kyiv (Ukraine) and LTD «Ophthalmological Clinic «World of Vision», Kiev (Ukraine). The control group included 25 people aged 45 to 79 years who did not have diabetes and were examined for cataracts. The study was prospective,

cohort, case-control. All subjects received informed consent to participate in the study.

At the time of the initial examination and after 1 year, all patients underwent conventional ophthalmological examinations, which included visometry, refractometry, tonometry, static perimetry, gonioscopy, biomicroscopy, and ophthalmoscopy. Ophthalmoscopy was performed using an aspherical Volk Super/Field lens (NC, USA) and a Goldman three-mirror contact lens. Also, all patients underwent spectral domain optical coherence tomography (OCT) on the device Optical Coherence Tomography 3D OCT-1000 (protocol Retina3D, RetinaRaster); also used OCT in the «Angio» mode (RetinaAngio protocol, wide 6x6 mm). Examination of the fundus was performed on a fundus camera, if necessary – with photography in 7 standard fields in accordance with the modified ETDRS system of clinical signs Airlie House [11]. The photographs studied the unified clinical signs of DR: MA and MH, IRMA, retinal venous abnormalities and retinal non-perfusion.

The level of EMAP-II was determined by enzyme-linked immunosorbent assay using BioSource reagent kits (USA) in blood plasma. Blood sampling was performed from the ulnar vein on an empty stomach in the level of 3 ml once at the time of the initial examination.

MedStat and MedCalc v.15.1 (MedCalc Software byba) software packages were used for statistical research. The mean (M) and its standard deviation (SD) were calculated. Frequency (%) and its standard error (SE,%) were used for qualitative characteristics. In all cases, the differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

In this study, patients were divided into two groups (Table 1). In the 1st group (72.5% of people) at the beginning of the study DNPR was not in both eyes – paired eyes had no signs of diabetic damage, the ETDRS level was 10, which corresponded to the stage of “no retinopathy” [11]. The second group (27.5%) included patients who did not have DNPR in one eye (“no retinopathy” stage) and in the other – there were single vascular changes (ETDRS level was 14 or 15).

There was no difference between groups of patients by age and sex ($p = 0.201$ and $p = 0.676$, respectively). The

Table 1

Distribution of patients by groups

Groups of patients	Age, years	Sex		Disease duration, Years
		Male	Female	
Control	65,12 $\pm$ 9,02	40,0 $\pm$ 9,8%	60,0 $\pm$ 9,8%	-
1st	68,41 $\pm$ 7,78	30,3 $\pm$ 5,7%	69,7 $\pm$ 5,7%	4,20 $\pm$ 2,23
2nd	66,76 $\pm$ 7,39	32,0 $\pm$ 9,3%	68,0 $\pm$ 9,3%	7,16 $\pm$ 1,11
Intergroup comparisons	F=1,62; p=0,201	$\chi^2=0,78$; p=0,676		t=6,35; p<0,001

Notes: data display format: quantitative – M $\pm$ SD; nominal – % $\pm$ SE; F – Fisher’s test for analysis of variance (ANOVA); χ^2 – Pearson’s criterion for comparing data distribution frequencies; t – Student’s criterion for independent samples; p – probability of differences (taken at $p < 0,05$).

duration of the disease was significant: patients in 2nd group (with the presence of diabetic retinal changes in one of the eyes) were sick, on average, three years longer, than those who did not have diabetic changes in the fundus ($p<0,001$). Analysis of carbohydrate metabolism showed a higher glycemia level in patients of 2nd group: 9.34 ± 1.86 mmol/l against 7.87 ± 2.15 mmol/l in 1st group ($p=0.016$).

Thus, the analysis of clinical and laboratory parameters showed that the initial manifestations of diabetic retinal lesions appeared in 27.5% of patients after 7.16 ± 1.11 years, and were accompanied by higher glycemia.

The blood EMAP-II level in DM2 patients was many times higher than in the control (table. 2). Moreover, in patients without retinal changes – in 3.7 times, and in patients with initial manifestations of diabetic retinal lesions – in 5.2 times ($p<0.001$).

The difference between the patients groups was statistically significant (Fig. 1): in the 2nd group it was 1.4 times higher than in the 1st ($p<0.001$). This result confirmed the association of an increase in EMAP-II level with diabetic manifestations of retinal damage.

The next step was to examine the association of progression of diabetic retinal changes over 1 year with EMAP-II levels. Progression was understood as changes in the fundus towards deterioration with the

Fig. 1. The blood EMAP-II level in patients by groups. Probable differences are marked above the columns of the diagrams: C – with the control; 1 – with the 1st group (in all cases $p<0,001$).

development of diabetic vascular changes where they did not exist, either initial (ETDRS level 20) or moderate (ETDRS levels 35, 43, 47) DNPR (Table 3). In 1st group, progression was observed in 50.0% of patients, while in 2nd group – in 92.0% ($p<0.001$), which indicated

Table 4

Blood EMAP-II level depending on the degree of progression of diabetic retinal changes after 1 year of observation (M±SD)

Indexes	Diabetic changes are absent (n=90)	Diabetic changes are present (n=92):			Intergroup comparisons
		single vascular abnormalities	initial DNPR	moderate DNPR	
		1	2	3	
EMAP-II, ng/ml	3,723±1,126	4,142±1,241	3,967±1,203	6,424±1,030	F=62,45; $p<0,001$
Post-hoc	1	–	p=0,604	p=0,882	–
	2	–	–	p=0,955	
	3	–	–	p<0,001	

Notes: data display format: M±SD; F – Fisher's test for analysis of variance (ANOVA); the Post-hoc lines show the probability of differences for paired (a posteriori) comparisons between these groups (1, 2, 3, 4) according to the Tukey HSD test for unequal in size samples; p – probability of differences (taken at $p<0,05$)

Table 2

Blood EMAP-II level by patient groups (M±SD)

Indexes	Control	Groups of patients		Intergroup comparisons
		1st	2nd	
EMAP-II, ng/ml	1,089±0,463	4,066±1,353	5,654±1,671	F=81,01; $p<0,001$
Post-hoc	Control	p<0,001	p<0,001	–
	1st group	–	p<0,001	

Notes: data display format: M±SD; F – Fisher's test for analysis of variance (ANOVA); the Post-hoc lines show the probability of differences for paired (a posteriori) comparisons between these groups according to the Tukey HSD test for unequal-sized samples; p – probability of differences (taken at $p<0,05$).

Table 3

Progression of diabetic retinal changes in groups of patients after 1 year

Progression:	Groups of patients		Intergroup comparisons
	1st	2nd	
is present (n=56)	50,00±6,15 %	92,00±5,43 %	$\chi^2=13,52$; $p<0,001$
is absence (n=35)	50,00±6,15 %	8,00±5,43 %	

Notes: data display format: %±SE; χ^2 – Pearson's criterion for comparing data distribution frequencies; p – probability of differences (taken at $p<0,05$).

Fig. 2. The blood EMAP-II level in the control group (Control) and in patients with absence («No») and with presence («Yes») of progression. Probable differences are marked above the columns of the diagrams: C – with the control group; N – with patients without progression (in all cases $p < 0.001$).

a significant tendency to progress in the presence of previous retinal damage in one of the eyes.

According to the presence or absence of progression, the level of EMAP-II was analyzed (Fig. 2). It was found that its level was 1.5 times higher ($p < 0.001$) in the presence of progression of diabetic retinal changes than without them.

The EMAP-II level in the presence of diabetic retinal changes, as expected, significantly exceeded that in the control group (3.6-5.9 times; $p < 0.001$). Among patients with different stages of DNPR, the maximum cytokine level was observed in the presence of moderate DNPR, while in patients with single vascular abnormalities (ETDRS 14/15) and initial DNPR (ETDRS 20), it was not significantly different ($p = 0.955$).

Thus, stratification by the degree of diabetic retinal vascular changes after 1 year of observation showed the dependence of their severity on the initial blood EMAP-II level – the cytokine level in the initial DNPR was increased 3-4 times, while its highest level was observed in moderate DNPR (in 5.9 times). Interestingly, in patients without diabetic retinal changes, the level of EMAP-II was significantly increased. This confirms the primacy of the cytokine level shift in relation to the occurrence and progression of diabetic retinal changes.

Thus, the study found, firstly, – a significant increase in blood EMAP-II in DM2, and, secondly, – the dependence of the initial diabetic retinal changes and the degree of their progression after 1 year on the EMAP-II level increase. These results suggest an important role of this cytokine for the development of DNPR. The degree of increase in its level in the blood is a factor that precedes the development of DNPR, and there is a certain dose dependence of this effect.

The basis of microvascular abnormalities in chronic hyperglycemia in DM2 are mechanisms, such as enzymatic and non-enzymatic glycation of proteins, activation of the polyols shunt, which leads to intracellular edema, intensification of oxidative stress, activation of protein-kinase C [18]. Due to the thickening and loosening of intercellular matrix proteins of connective tissue and the basement membrane of capillaries, chronic inflammation is their hyalinization, which leads to loss of pericytes, destruction of endothelial cells and atrophy of capillaries. These pathological processes are combined into the concept of diabetic vasoregression, which determines the formation of DNPR from the first years of the disease [19].

The progression of pathological changes leads to sectoral occlusion of blood vessels and the formation of ischemic foci in the form of soft exudates, IRMA, MA and other manifestations characteristic of DNPR [20]. At this stage of the pathological process, the development of spontaneous MH, the source of which is damaged vessels of the microcirculatory rate.

In this light, it can be assumed that one of the causes of vasoregression is the activation of EMAP-II formation, which in the early stages is a compensatory response of retinal tissues to hypoxia and chronic inflammation caused by accumulation of Advance Glycation End Products (AGE) and oxidative stress [21]. Subsequently, the accumulation of EMAP-II can become a factor of damage. This assumption is confirmed in the results of this study.

Discussing the pathogenic effects of excessive accumulation of EMAP-II, in the first place we can note endothelial damage. It has been shown that under hypoxia, it increases the sensitivity of endothelial cells to apoptosis by activating the vesicular transport of TNF-R1 receptors to the cell membrane and facilitating the transmission of apoptotic signals by mobilization and membrane expression of the TNF-R1-Associated Death Domain [22]. In addition, EMAP-II enhances the expression of TNF-R1 by endothelial cells both in vitro and in vivo, which causes sensitization of the endothelium to the action of TNF [23]. This explains the close relationship between endothelial dysfunction and chronic inflammation in the pathogenesis of DNPR. Moreover, the specific effects of EMAP-II, which determine its antiangiogenic properties, at this stage contribute to the development of changes characteristic of DNPR and may inhibit the further development of proliferative diabetic retinopathy. The latter is associated with inhibition of VEGF and HIF-1 α production, which may inhibit neoangiogenesis.

Results similar to those obtained in this work were highlighted in the study [24]. Serum EMAP-II levels were significantly elevated in patients with type 1 diabetes, especially in the presence of microvascular complications. At the same time, EMAP-II levels were directly related to inflammation, glycemic control, albuminuria and the risk of microvascular complications.

Also in DM2, a significant increase in the blood of EMAP-II level was found, which the author associates with the development of endothelial dysfunction due to chronic hyperglycemia [25]. The increase in EMAP-II level was directly correlated with the level of glycosylated hemoglobin, blood glucoses level, body mass index, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides.

CONCLUSIONS

1. The blood EMAP-II level in DM2 was many times higher than in the control, which depended on the presence of diabetic retinal vascular changes: in patients without retinal changes ("no retinopathy") – 3.7 times, and in patients with single retinal vascular abnormalities (ETDRS 14/15) – 5.2 times ($p < 0.001$).

2. The initial blood EMAP-II level was associated with the progression of diabetic retinal changes after 1 year – in their presence it was 1.5 times higher than without them ($p < 0.001$).

3. Stratification at the DNPR stages after 1 year also showed the dependence of the diabetic retinal changes severity on the initial EMAP-II level: in the presence of single vascular abnormalities and initial DNPR, it was increased 3-4 times, while in moderate DNPR – 5.9 times ($p < 0.001$ for all comparisons).

REFERENCES

- Heidemann C., Paprott R., Stühmann L.M., Baumert J., Mühlenbruch K., Hansen, Schiborn C., Zahn D., Gellert P., Scheidt-Nave Ch. Perceived diabetes risk and related determinants in individuals with high actual diabetes risk: results from a nationwide population-based survey. *BMJ. Open Diabetes Res Care*. 2019 Jun 21; 7(1):e000680. doi: 10.1136/bmjdr-2019-000680.
- Khan R.M., Chua Z.J., Tan J.C., Yang Y., Liao Z., Zhao Y. From pre-diabetes to diabetes: diagnosis, treatments and translational research. *Medicina*. Kaunas. 2019 Aug 29; 55(9): 546. doi: 10.3390/medicina55090546.
- Lotfy M., Adeghate J., Kalasz H., Singh J., Adeghate E. Chronic complications of diabetes mellitus: a mini review. *Curr Diabetes Rev*. 2017; 13(1):3-10. doi: 10.2174/1573399812666151016101622.
- Davies M.J., D'Alessio D.A., Fradkin J., Kernan W.N., Mathieu C., Mingrone G., Rossing P., Tsapas A., Wexler D.J., Buse J.B. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018 Dec; 41(12):2669-701. doi: 10.2337/dci18-0033.
- Tronko M.D. [Priority issues of diabetology in Ukraine at the present stage and ways to solve them]. 2020 [Internet]. [cited 20.10.2020]. [in Ukrainian]. Available on: http://iem.net.ua/endocrinology_task/
- International Diabetes Federation and The Fred Hollows Foundation. Diabetes eye health: A guide for health care professionals. Brussel, Belgium: International Diabetes Federation [Internet]; 2015 [cited 15.07.20]; p. 10. Available on: <https://idf.org/our-activities/care-prevention/eye-health/eye-health-guide.html#sub-content-tab-nav>.
- Nowak M.S., Grzybowski A. Review of the epidemiology of diabetic retinopathy [Internet]. *Modern Retina*. Ophthalmology Times. 2018 June 11. Available on: <https://www.modernretina.com/diabetic-retinopathy/review-epidemiology-diabetic-retinopathy>.
- Kirsch S, Iroku-Malizi T. Eye conditions in older adults: diabetic retinopathy. *FP Essent*. 2016 Jun; 445:29-37; quiz 38-9. PMID: 27348530. Available on: <https://pubmed.ncbi.nlm.nih.gov/27348530/>
- Safi H., Safi S., Ali H.-M., Hamid A. Early detection of diabetic retinopathy. *Survey of Ophthalmology*. 2018 Apr; 63 (5): 601-8. doi: 10.1016/j.survophthal.2018.04.003.
- Voigt M., Schmidt S., Lehmann T., Köhler B., Kloos C., Voigt U.A., Meller D., Wolf G., Müller U.A., Müller N. Prevalence and Progression Rate of Diabetic Retinopathy in Type 2 Diabetes Patients in Correlation with the Duration of Diabetes. *Exp Clin Endocrinol Diabetes*. 2018 Sep; 126(9):570-6. doi: 10.1055/s-0043-120570.
- Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs – an extension of the modified Airlie house classification: ETDRS report № 10. *Ophthalmology*. 2020 Apr; 127(4S): 99-119. doi: 10.1016/j.ophtha.2020.01.030.
- van Horssen R., Eggermont A.M., ten Hagen T.L. Endothelial monocyte-activating polypeptide-II and its functions in (patho)physiological processes. *Cytokine Growth Factor Rev*. 2006 Oct; 17(5):339-48. doi: 10.1016/j.cytogfr.2006.08.001.
- Mogilynytska L.A. [Endothelial monocyte-activating polypeptide-II: properties, functions, and pathogenetic significance]. *Fiziol. Zh*. 2015; 61(1): 102-11. doi: 10.15407/fz61.01.102 [in Ukrainian]
- Awasthi N., Schwarz M.A., Verma V., Cappiello C., Schwarz R.E. Endothelial monocyte activating polypeptide II interferes with VEGF-induced proangiogenic signaling. *Lab Invest*. 2009 Jan; 89(1):38-46. doi: 10.1038/labinvest.2008.106.
- Tandle A.T., Calvani M., Uranchimeg B., Zahavi D., Melillo G, Libutti SK. Endothelial monocyte activating polypeptide-II modulates endothelial cell responses by degrading hypoxia-inducible factor-1alpha through interaction with PSMA7, a component of the proteasome. *Exp Cell Res*. 2009 Jul 1; 315(11):1850-9. doi: 10.1016/j.yexcr.2009.03.021.
- Matschurat S., Knies U.E., Person V., Fink L., Stoelcker B., Ebenebe C., Behrendorf H.A., Schaper J., Clauss M. Regulation of EMAP II by hypoxia. *Am J Pathol*. 2003 Jan; 162(1):93-103. doi: 10.1016/S0002-9440(10)63801-1.
- Lee D.D., Hochstetler A., Murphy C., Lowe C.W., Schwarz M.A. A distinct transcriptional profile in response to endothelial monocyte activating polypeptide

- II is partially mediated by JAK-STAT3 in murine macrophages. *Am J Physiol Cell Physiol.* 2019 Sep 1; 317(3):C449-C456. doi: 10.1152/ajpcell.00277.2018.
18. Eshaq R.S., Aldalati A.M.Z., Alexander J.S., Harris N.R. Diabetic retinopathy: Breaking the barrier. *Pathophysiology.* 2017; 24(4):229-41. doi: 10.1016/j.pathophys.2017.07.001.
 19. Gupta A., Bhatnagar S. Vasoregression: A shared vascular pathology underlying macrovascular and microvascular pathologies? *OMICS.* 2015 Dec; 19(12):733-53. doi: 10.1089/omi.2015.0128.
 20. Balashevich L.I. & Izmailov A.S. [Diabetic ophthalmopathy]. S-Pb.: Man, 2012. 396 p. [in Russian]. Available on: <http://ophthalmobook.com.ua/knigi/oftalmologiya/diagnostika/diabeticheskaya-oftalmopatiya.html>
 21. Xu J., Chen L.J., Yu J., Wang H.J., Zhang F., Liu Q., Wu J. Involvement of advanced glycation end products in the pathogenesis of diabetic retinopathy. *Cell Physiol Biochem.* 2018; 48(2):705-717. doi: 10.1159/000491897.
 22. van Horssen R., Rens J.A., Schipper D., Eggermont A.M., ten Hagen T.L. EMAP-II facilitates TNF-R1 apoptotic signalling in endothelial cells and induces TRADD mobilization. *Apoptosis.* 2006 Dec; 11(12):2137-45. doi: 10.1007/s10495-006-0284-5.
 23. Berger A.C., Alexander H.R., Wu P.C., Tang G., Gnant M.F., Mixon A., Turner E.S., Libutti S.K. Tumour necrosis factor receptor I (p55) is upregulated on endothelial cells by exposure to the tumour-derived cytokine endothelial monocyte-activating polypeptide II (EMAP-II). *Cytokine.* 2000 Jul; 12(7):992-1000. doi: 10.1006/cyto.2000.0687.
 24. Adly A.A.M., Ismail E.A., Tawfik L.M., Ebeid F.S.E., Hassan A.A.S.. Endothelial monocyte activating polypeptide II in children and adolescents with type 1 diabetes mellitus: Relation to micro-vascular complications. *Cytokine.* 2015 Dec; 76(2):156-162. doi: 10.1016/j.cyt.2015.06.006.
 25. Mohyl'nyts'ka L.A. Serum levels of endothelial monocyte-activating polypeptide-II in type 2 diabetes mellitus. *Fiziol. Zh.* 2014; 60(1): 84-90. doi: <https://doi.org/10.15407/fz60.01.084>.

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ЗВ'ЯЗОК З ПРОГРЕСИЄЮ ДІАБЕТИЧНОЇ НЕПРОЛІФЕРАТИВНОЇ РЕТИНОПАТІЇ ПРИ ЦУКРОВОМУ ДІАБЕТІ 2-го ТИПУ ВМІСТУ У КРОВІ ЕНДОТЕЛІАЛЬНОГО МОНОЦИТАКТИВУЮЧОГО ПОЛІПЕПТИДУ-II

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Актуальність. Чисельні прозапальні та антиангіогенні властивості ендотеліального моноцитаактивуючого поліпептиду-II (EMAP-II) дозволяють припустити його можливу роль у виникненні та прогресуванні діабетичної непроліферативної ретинопатії (ДНПР) при цукровому діабеті 2 типу (ЦД2).

Мета: визначити вміст у крові пацієнтів на ЦД2 ЕМАР-II та встановити його зв'язок з прогресією ДНПР.

Матеріали та методи. Було обстежено 91 пацієнта з ЦД2Т (182 ока), яких розподілили на групи: 1 (n=66) – ДНПР не було на обох очах і 2 (n=25) – у яких на одному оці діабетичних змін не було, а на іншому були відмічені поодинокі судинні аномалії (рівень ETDRS 14, 15). До контрольної групи було залучено 25 осіб відповідного віку та статі. Повторно пацієнтів обстежували через 1 рік. Вміст ЕМАР-II визначали імуноферментним методом у плазмі крові одноразово на початку дослідження. Для статистичних досліджень використано статпакети MedStat і MedCalc v.15.1 (MedCalc Software bvba).

Результати. Аналіз клініко-лабораторних показників показав, що початкові прояви діабетичного ураження сітківки проявлялися у 27,5% пацієнтів через $7,16 \pm 1,11$ років, та супроводжувалися більшою гікемією. Вміст ЕМАР-II при ЦД2 був багаторазово збільшеним у порівнянні з контролем, що залежало від наявності діабетичних судинних змін сітківки: у пацієнтів без змін сітківки (1 група) – у 3,7 рази, а у пацієнтів з поодинокими судинними аномаліями сітківки (2 група) – у 5,2 рази ($p < 0,001$). Вміст ЕМАР-II на початку дослідження був пов'язаний з прогресією діабетичних змін сітківки через 1 рік – за їх наявністю він був у 1,5 рази більшим, ніж без таких ($p < 0,001$). Стратифікація за стадією ДНПР через 1 рік також показала залежність вираженості діабетичних змін сітківки від початкового вмісту ЕМАР-II: при наявності поодиноких судинних аномалій та початковій ДНПР він був збільшений у 3-4 рази, тоді як при помірній ДНПР – у 5,9 рази ($p < 0,001$ для всіх порівнянь).

Висновок. Встановлено суттєве збільшення вмісту ЕМАР-II при ЦД2 та залежність початкових діабетичних змін сітківки та ступеню їх прогресії через 1 рік від приросту вмісту ЕМАР-II у крові.

Ключові слова: діабетична непроліферативна ретинопатія, цукровий діабет 2 типу, ЕМАР-II

СВЯЗЬ ПРОГРЕССИИ ДИАБЕТИЧЕСКОЙ НЕПРОЛИФЕРАТИВНОЙ РЕТИНОПАТИИ ПРИ САХАРНОМ ДИАБЕТЕ 2-ГО ТИПА С СОДЕРЖАНИЕМ В КРОВИ ЭНДОТЕЛИАЛЬНОГО МОНОЦИТАКТИВИРУЮЩЕГО ПОЛИПЕПТИДА-II

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Актуальность. Многочисленные провоспалительные и антиангиогенные свойства эндотелиального моноцитаактивирующего полипептида-II (ЕМАР-II) позволяют предположить его возможную роль в возникновении и прогрессировании диабетической непролиферативной ретинопатии (ДНПР) при сахарном диабете 2 типа (СД2Т).

Цель – определить содержание в крови пациентов с СД2Т ЕМАР-II и установить его связь с прогрессией ДНПР.

Материалы и методы. Обследован 91 пациент с СД2Т (182 глаза), которых распределили на группы: 1 (n=66) – ДНПР не было на обоих глазах, и 2 (n=25) – на одном глазу диабетических изменений не было, а на другом были отмечены единичные сосудистые аномалии (уровень ETDRS 14, 15). В контрольную группу вошли 25 пациентов соответствующего возраста и пола. Повторно пациентов обследовали через 1 год. Содержание ЕМАР-II определяли иммуноферментным методом в плазме крови однократно в начале исследования. Для статистических исследований использованы статпакеты MedStat и MedCalc v.15.1 (MedCalc Software bvba).

Результаты. Анализ клинико-лабораторных показателей показал, что начальные проявления диабетического поражения сетчатки проявлялись у 27,5% пациентов через $7,16 \pm 1,11$ лет и сопровождалась большей гликемией. Содержание ЕМАР-II при СД2Т было многократно увеличенным по сравнению с контролем, что зависело от наличия диабетических сосудистых изменений сетчатки: у пациентов без изменений сетчатки (1 группа) – в 3,7 раза, а у пациентов с начальными сосудистыми аномалиями (2 группа) – в 5,2 раза ($p < 0,001$). Содержание ЕМАР-II в начале исследования было связано с прогрессией диабетических изменений сетчатки через 1 год – при их наличии оно было в 1,5 раза больше, чем без таковых ($p < 0,001$). Стратификация по стадии ДНПР через 1 год также показала зависимость выраженности диабетических изменений сетчатки от начального содержания ЕМАР-II: при наличии единичных сосудистых аномалий и начальной ДНПР он был увеличен в 3-4 раза, тогда как при умеренной ДНПР – в 5,9 раза ($p < 0,001$ для всех сравнений).

Вывод. Установлено существенное увеличение содержания ЕМАР-II при СД2Т и зависимость начальных диабетических изменений сетчатки и степени их прогрессии через 1 год от прироста содержания ЕМАР-II в крови.

Ключевые слова: диабетическая непролиферативная ретинопатия, сахарный диабет 2 типа, ЕМАР-II