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ANGIOGENESIS MODULATION AS AN EFFICIENT METHOD TO TREAT THE EXPERIMENTAL DIABETIC RETINOPATHY

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The purpose of the study was to investigate the changes in blood vascular endothelial growth factor levels in experimental animals with diabetic retinopathy modeling using the ways of its pharmacological correction. Experimental studies were performed on the model of streptozotocin-induced diabetes mellitus on Wistar rats which were randomized on seven groups in dependence of separate and combined pharmacological compounds administration to treat the experimental diabetic retinopathy features. The vascular endothelial growth factor level in the blood serum of rats was determined on 30, 60 and 180 days of the trials. The data obtained confirm the development of diabetic retinopathy in conditions of streptozotocin model of diabetes mellitus. Diabetic retinopathy development characterized by vascular endothelial growth factor content in rats blood increase with the top level of increase on the 180th day of the trials. The expressed positive effect of vascular endothelial growth factor level normalization was observed in case of aflibercept, L- arginine and citicoline combined administration. The authors stressed on immune mechanisms pathogenetic role in diabetic retinopathy. Determination of vascular endothelial growth factor principal pathogenetic role in diabetic retinal tissue damage opened a new direction of diabetic retinopathy targeted pathogenetically determined pharmacocorrection by blocking the vascular endothelial growth factor signaling pathway. The established immune mechanisms involvement into diabetic retinopathy pathogenetic mechanisms by blood vascular endothelial growth factor level increase is an experimental background of reasonability of vascular endothelial growth factor both synthesis and/or activity block in clinical conditions.

Key words: diabetes mellitus, experimental diabetic retinopathy, retinal ischemia, vascular endothelial growth factor, pathogenetic pharmacological correction.

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МОДУЛЯЦІЯ АНГІОГЕНЕЗУ ЯК ЕФЕКТИВНИЙ МЕТОД ЛІКУВАННЯ ЕКСПЕРИМЕНТАЛЬНОЇ ДІАБЕТИЧНОЇ РЕТИНОПАТІЇ

Метою дослідження було вивчення змін вмісту фактора росту ендотелію судин у крові експериментальних тварин за умов діабетичної ретинопатії шляхом її фармакологічної корекції. Експериментальні дослідження проводили на моделі стрептозотоцин-індукованого цукрового діабету на щурах лінії Вістар, які були розділені на сім груп залежно від окремого та сумісного введення фармакологічних сполук для лікування ознак експериментальної діабетичної ретинопатії. Рівень фактора росту ендотелію судин у сироватці крові щурів визначали на 30, 60 та 180 добу досліду. Отримані дані підтверджують розвиток діабетичної ретинопатії в умовах стрептозотоцинової моделі цукрового діабету. Розвиток діабетичної ретинопатії характеризується підвищенням вмісту фактора росту ендотелію судин у крові щурів з максимальним рівнем його підвищення на 180 добу досліду. Виражений позитивний ефект нормалізації рівня фактора росту ендотелію судин спостерігався при сумісному введенні афліберцепту, L-аргініну та цитиколіну. Автори наголошують на патогенетичній ролі імунних механізмів у розвитку діабетичної ретинопатії. Визначення основної патогенетичної ролі фактора росту ендотелію судин у пошкодженні тканини сітківки при цукровому діабеті відкрило новий напрям спрямованої патогенетично детермінованої фармакокорекції діабетичної ретинопатії шляхом блокування сигнального шляху фактора росту ендотелію судин. Доведене залучення імунних механізмів до патогенетичних механізмів діабетичної ретинопатії підвищенням рівня фактора росту ендотелію крові є експериментальним підґрунтям доцільності блокування синтезу та/або активності фактора росту судинного ендотелію в клінічних умовах.

Ключові слова: цукровий діабет, експериментальна діабетична ретинопатія, ішемія сітківки, фактор росту ендотелію судин, патогенетична фармакокорекція.

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According to WHO data, diabetic retinopathy (DR) is the main cause of vision loss and blindness in diabetes [8, 12]. Vascular endothelial growth factor (VEGF) content in blood serum was established to be informative as marker of DR development [5]. In the retina, under the influence of VEGF in conditions of hypoxia and with the participation of proteases, the initial stages of angiogenesis occur migration of endothelial cells in the extracellular matrix and degradation of the basal membrane of the capillary endothelium. VEGF regulates the development of newly formed vessels to the stage of involvement of pericytes, which stabilize the vascular network [2, 14]. Also, the vascular growth factor stimulates increased permeability of the vascular wall, disruption of the hematoretinal barrier functions due to the phosphorylation of tight junctions of endotheliocytes [9]. An increase in the permeability of

the hematoretinal barrier leads to the development of diabetic macular edema. VEGF causes increased expression of leukocyte adhesion molecules $VCAM_1$, $ECAM_1$, PECAM-1, P-selectin, which in turn increase leukocyte adhesion in retinal microvessels. As a result, there is a violation of the permeability of the hematoretinal barrier, loss of endotheliocytes, infiltration of the retina with leukocytes, and diapedesis [2, 6].

A network of endotheliocytes formed during vasculogenesis serves as a framework for angiogenesis [3, 11, 15]. Inadequate angiogenesis is the basis of such a pathological process as proliferative diabetic retinopathy. The causes of a progressive decrease in visual acuity in patients with diabetes are the excessive proliferation of vessels in the eyeball. An imbalance between inhibitors and stimulators of angiogenesis is characteristic of the development of DR. During retinal ischemia, hyperproduction of VEGF increases, which plays a key role in the activation of pathological neoplasms [7, 11].

The purpose of the study was to investigate the changes in blood vascular endothelial growth factor levels in experimental animals with diabetic retinopathy modeling using the ways of its pharmacological correction.

Materials and methods. Experimental trials were performed on 420 white male rats weighing 180–200 g. The animals were kept in standard vivarium conditions. Experimental animals keeping, handling and manipulation was carried out in accordance with the "International Code of Medical Ethics" (Venice, 1983), the "General Ethical Principles of Animal Experiments" adopted by the "General Ethical Principles of Animal Experiments" adopted by the Fifth National Congress on Bioethics (Kyiv, 2013) and was guided by the recommendations of the European Convention for the Protection of Vertebrate Animals for Experimental and Other Scientific Purposes (Strasbourg, 1986), Directive 2010/63/EU of the European Parliament and Council on protecting animals used for scientific purposes and guidelines of the of Ukraine "On protection of animals from cruel treatment" No. 440-IX of 14 January 2020.

Experimental animals were randomized as follows. Group 1 – intact animals; group 2 – rats with DR without correction; group 3 – rats with DR with hyperglycemia correction using metformin (*per os*, 300 mg/kg; "Merck Sante", France); group 4 – rats with DR with hyperglycemia correction using L- arginine (*per os*, 500 mg/kg; "SIMESTA", quality standard USP32; China) and aflibercept (subconjunctival injections, 0.08 ml [25 mg/ml]; "Bayer AG", Germany); group 5 – rats with DR with hyperglycemia correction using aflibercept and bromfenak (subconjunctival injections, 0.09 %; "Sentiss Pharma Pvt. Ltd", India); group 6 – rats with DR with hyperglycemia correction using aflibercept, bromfenak and L-carnitine (*per os*, 2.5 mg/kg; "Sigma-Aldrich Chemie GmbH", Germany); group 7 – rats with DR with hyperglycemia correction using aflibercept, L-arginine and citicoline (i.m., 81.8 mg/kg [0.33 ml/kg]; "Halychpharm", Ukraine). Each group consists of 60 rats.

Diabetes Mellitus type II and DR were modeled by streptozotocin (STZ; i.p., 66 ml/kg; "Sigma-Aldrich Chemie GmbH", Germany) administration dissolved in 0.1 M citrate buffer (pH=4.5). Dose of STZ was preceded by a high-fat diet for 28 days and was divided into two injections.

Metformin and L-arginine (both compounds before injections were dissolved 0.9 % sodium chloride solution), bromfenak, L-carnitine and citicoline were administered once per day. Aflibercept (anti-VEGF therapy) was administered with an interval of 1 injection every 30 days of a trial.

The experimental trials were divided into the following three stages: stage 1 lasted 30 days till the end of DM modeling (after STZ the second dose administration); stage 2 lasted 30 days till the 60^{th} day after DM modelling; stage 3 lasted 120 days till the 180^{th} day after DM modelling.

Animals were euthanized by decapitation (using a guillotine after 30, 60 and 180 days). Blood was taken from the retroorbital venous plexus using a glass pipette with a pulled capillary whose tip is pointed at an angle of 45°. The VEGF level in the blood serum of rats was determined immunoenzymatically with the sets of reagents.

The data obtained were presented as mean (M) and the standard error of the mean (m) and were calculated statistically using nonparametric Mann-Whitney U-test. The minimum statistical probability was determined at $p<0.05$.

Results of the study and their discussion. The VEGF level was increased at the 1^{st} stage in group 2 (DR without correction) compared to the same control index of 67.8 % ($p<0.001$; Table 1).

At stage 2, an increase in the studied index was found at 121 % compared to the intact group, and 38.8 % ($p<0.001$) compared to its value at the previous stage. At stage 3 it was established that VEGF level was 144.9 % higher compared to the intact group, on 52.4 % higher than the value on stage 1, and 9.8 % – on stage 2 (in all cases $p<0.001$).

Table 1

VEGF level in the blood of animals with diabetic retinopathy and different methods of correction during the whole trial

Groups of animals	The value of VEGF index in blood samples (M±m), (μM/l)					
	Stage 1 (A), the 30th day		Stage 2 (B), the 60th day		Stage 3 (C), the 180th day	
Group 1	28.9±0.44		30.45±0.5		30.19±0.51	
	-	-	1A-1B	p<0.05	1A-1C 1B-1C	p>0.05 p>0.05
Group 2	48.5±0.4		67.32±0.42		73.94±0.38	
	1A-2A	p<0.001	1B-2B 2A-2B	p<0.001 p<0.001	1C-2C 2A-2C 2B-2C	p<0.001 p<0.001 p<0.001
Group 3	42.93±0.5		50.75±0.42		54.12±0.43	
	1A-3A 2A-3A	p<0.001 p<0.001	1B-3B 2B-3B 3A-3B	p<0.001 p<0.001 p<0.001	1C-3C 2C-3C 3A-3C 3B-3C	p<0.001 p<0.001 p<0.001 p<0.001
Group 4	39.46±0.32		37.97±0.34		34.48±0.43	
	1A-4A 2A-4A 3A-4A	p<0.001 p<0.001 p<0.001	1B-4B 2B-4B 3B-4B 4A-4B	p<0.001 p<0.001 p<0.001 p<0.01	1C-4C 2C-4C 3C-4C 4A-4C 4B-4C	p<0.001 p<0.001 p<0.001 p<0.001 p<0.001
Group 5	41.27±0.43		40.65±0.61		38.92±0.53	
	1A-5A 2A-5A 3A-5A 4A-5A	p<0.001 p<0.001 p<0.05 p<0.01	1B-5B 2B-5B 3B-5B 4B-5B 5A-5B	p<0.001 p<0.001 p<0.001 p<0.001 p>0.05	1C-5C 2C-5C 3C-5C 4C-5C 5A-5C 5B-5C	p<0.001 p<0.001 p<0.001 p<0.001 p<0.01 p<0.05
Group 6	38.28±0.48		36.67±0.46		35.29±0.43	
	1A-6A 2A-6A 3A-6A 4A-6A 5A-6A	p<0.001 p<0.001 p<0.001 p<0.05 p<0.001	1B-6B 2B-6B 3B-6B 4B-6B 5B-6B 6A-6B	p<0.001 p<0.001 p<0.001 p<0.05 p<0.001 p<0.05	1C-6C 2C-6C 3C-6C 4C-6C 5C-6C 6A-6C 6B-6C	p<0.001 p<0.001 p<0.001 p>0.05 p<0.001 p<0.001 p<0.05
Group 7	33.52±0.43		31.65±0.41		30.45±0.52	
	1A-7A 2A-7A 3A-7A 4A-7A 5A-7A 6A-7A	p<0.001 p<0.001 p<0.001 p<0.001 p<0.001 p<0.001	1B-7B 2B-7B 3B-7B 4B-7B 5B-7B 6B-7B 7A-7B	p>0.05 p<0.001 p<0.001 p<0.001 p<0.001 p<0.001 p<0.01	1C-7C 2C-7C 3C-7C 4C-7C 5C-7C 6C-7C 7A-7C 7B-7C	p>0.05 p<0.001 p<0.001 p<0.001 p<0.001 p<0.001 p<0.001 p>0.05

Group 3 at the first stage revealed the investigated index to be by 48.5 % higher than the same control data, and compared to group 2, it was lower on 11.5 %. At stage 2, an increase in VEGF is observed, its level is higher both compared to the intact group – by 66.7 % and compared to the previous stage – on 18.2 %, being compared to group 2 it is lower by 24.6 % (in all cases p<0.001). At stage 3, a more pronounced increase in VEGF compared to the intact group was established – by 79.2 % (p<0.001). It was higher by 26 % compared to same data on stage (p<0.001), on stage 2 – by 6.6 %, but being compared to group 2, its increase is less pronounced - by 26.8 % (p<0.001).

An increase of VEGF index was found in the group 4 at stage 1 – by 36.5 % (p<0.001), and compared to groups 2 and 3 its values were less elevated – by 18.6 % (p<0.001) and by 8 %, respectively. The investigated index at stage 2 was increased by 24.7 % compared to the intact group (p<0.001). The increase in the marker is less pronounced relative to its value in group 2 – by 43.6 %, relative to group 3 – by 25.2 % and pertaining with its value in the previous stage – by 3.8 % (in all cases p<0.001). At stage3 the effect of this method of DR correction is even more pronounced: the level of the proliferation marker compared to the intact group is higher by 14.2 %, compared to group 2 it is lower on 53.4 % and with group

3 it is less pronounced – by 36.3 % (in all cases p<0.001). Also, its value is smaller compared to the analogous results in stage 1 – by 12.6 % and in stage 2 – by 9.2 % (in all cases p<0.001).

In group of rats with DR using aflibercept and bromfenac for hyperglycemia correction the following data were obtained. At stage1 the VEGF level was higher by 42.8 % (p<0.001) compared to the intact group and by 4.6 % (p<0.01) relative to group 4. In comparison with group 2, its increase is less pronounced - by 14.9 % (p<0.001), and in comparison, with group 3 – by 3.9 % (p<0.05). At stage 2 the VEGF level is higher by 33.5 % compared to the same the group1, but the increase is less pronounced compared to group 2 – by 39.6 %, compared to group 3 – by 19.9 % (in all cases p<0.001) and compared to analogous data at stage 1 – by 1.5 %. The investigated index increased by 7 % vs the same data in group 4 (p<0.001). VEGF increased on stage 3 by 28.9 % compared to group 1, and by 12.9 % compared to group 4 (in all cases p<0.001). Relatively to all subsequent groups, its increase is less pronounced – vs group 2 – by 47.4 %, vs group 3 – by 28 % (in all cases p<0.001), vs the same data on stage 1 – by 5.7 % (p<0.01) and vs the same data on stage 2 – by 4.3 % (p<0.05).

Blood VEGF level at stage 1 in rats of group 6 was higher on 32.4 % vs the same control data (p<0.001), and its rise was less pronounced relative to all other groups: by 21 % (p<0.001) vs group 2, by 10.83 % (p<0.001) vs group 3, by 3 % (p<0.05) vs group 4, by 7 % vs group 5 (p<0.001). The established positive trend was followed also at stages 2 and 3 of the trial which indicates the efficacy of this method of correction.

The most pronounced positive effect with blood VEGF level determination we observed in group 7 using combined aflibercept, L-arginine and citicoline administration. The VEGF level was higher on 15.9 % by stage 1 (p<0.001), relative to all other experimental groups its level is lower: vs groups 2-6 in the range between 12.4 % and 30.9 % (in all cases p<0.001).

At stage 2 the VEGF index was the same pertaining its control value (p>0.05). The index obtained was by 52.9 % less vs the same index in rats with DR without pharmacological correction (p<0.001). Its value is also lower compared with the same data in groups 3–6 (from 13.7 % to 37.6 %; in all cases p<0.001).

The analogous profile of antidiabetic efficacy we found while detected blood VEGF index at stage 3 of the trial.

Therefore, the data obtained showed the exact possibility of DR development in the course of DM that proved also by other experimental and clinical data [3, 5, 6, 8]. The main our idea was not to showed the evident vision function failure throughout chronic and complicated DM, but the indentify both the immune system involvement into the investigated pathological process and to check the antidiabetic efficacy of the proposed method of DR pathogenetic pharmacological correction. Methodologically we used with the pharmacological compounds with diverse well-known mechanisms of the corrective efficacy realization which also allowed us to make confident conclusions.

Consequently, with the purpose of obtained results discussing we can highlight the following several fundamental blocks. And, firstly, we want to summarize the data obtained during DR pharmacological correction. Hence, the blood VEGF data in group 2 confirm DR development, a significantly expressed studied index increase was detected on the 180th day of the trial. Analyzing data obtained in group 3 it was established that pathological condition correction using hypoglycemic agents has partial positive impact but requires the involvement of additional means of correction to normalize the level of glycemia.

The results of group 4 indicate that both NO donor and aflibercept using for DR correction has positive effect on blood VEGF level reduction, more pronounced vs the same in group 3 but it does not reach normal values. It is observed that the correction of the simulated pathological condition by reducing hyperglycemia, administration of aflibercept and bromfenac (group 5) gives positive results, but less pronounced, compared to the data of the 4th group.

It was found that in rats with DR with subsequent correction of hyperglycemia, administration of aflibercept, L-carnitine and bromfenac at stage 1, there is a pronounced efficacy of the used method of correction compared with the previously used methods, the established positive trend is being followed also at the 2nd and 3rd stages of experimental trials which indicates the proposed correction method efficacy.

The most pronounced positive effect of VEGF level normalization was observed when using a combined hypoglycemic drugs administration – aflibercept, L-arginine and citicoline.

Therefore, and secondly, we attract attention to the fact that the most expressed antidiabetic and corrective effect in the conditions of DR was obtained with the combined use of three pharmacological compounds – aflibercept, L-arginine and citicoline. Important that this original effect exceeded the

antidiabetic efficacy of the classical drug metformin in our trials which only strengthens the reasonability of our data prospective clinical testing in patients with DR.

Thirdly, it is important to trace the mechanism of the protective, retinoprotective and simultaneous antidiabetic effects of the used scheme of pharmacological correction.

The aflibercept action is well known to be related with neoangiogenesis suppression [10]. The mechanism of L-arginine action is its antioxidant efficacy and stimulation of NO synthesis which resultant effect is both systemic and cardiac bloodflow normalization [4]. The peptide drug citicoline has membrane stabilizing profile of action [6].

In this aspect, our data are particularly corresponded to results that have highlighted the antidiabetic efficiency of alpha-lipoic acid and vitamins due to their antioxidant influence [1, 13]. Interesting is that antidiabetic effects similar to those in citicoline, which highlight peptidergic mechanisms involvement into eye and the visual analyzer diabetic damage, were identified in case of sermion administration in experimental and conditions [1].

Fourthly, it is important to note the NO synthesis switch into an alternative way in experimental DR in rats with streptozotocin-induced diabetes, which characterizes by inducible NO synthase activity enhancement. Its activation via L-arginine revealed retinoprotective efficiency. This we explain by the enzyme ability to improve oxidative metabolism, through an enhanced mitochondrial function and to promote both insulin and glucagon the secretion.

It is understandable that both direct and indirect constitutive isoforms of NO-synthase blockade cause also antidiabetic effects in experimental and in clinical trials in patients with DR [1]. This effect proves the cells and organs diabetic damage direct mediation by nitratergic mechanisms.

Finally, the pathogenetic role of immune mechanisms involvement in DR, which has been shown by VEGF level increase, we considered to be an important result of our trials. Our data are reliable in a certain way with the results of patients with diabetic proliferative retinopathy clinical examinations, in which the VEGF content increase was detected in the aqueous humor and vitreous [12].

It is also interesting that VEGF gene expression activation was proved in conditions of experimental retina ischemic damage, resulting in VEGF-A level increase in retinal tissue [12]. The increase of VEGF content in conditions of retina ischemic damage is explained by this immune compound leading role in angiogenesis activation [8]. Determination of VEGF principal pathogenetic role in diabetic retinal tissue damage opened a new direction of the named pathological condition so-called targeted pathogenetically determined pharmacocorrection by blocking the VEGF signaling pathway, which achieves several mechanisms of angiogenesis inhibition. The authors prove the cessation of new vessels growth and the partial desolation of the existing ones. Additionally, a decrease in VEGF activity and content leads to apoptosis of endothelial cells of the vessels that feed the retina [10].

Consequently, we believe that the demonstrated immune mechanisms involvement into DR pathogenetic mechanisms by blood VEGF level increase is an experimental background of reasonability of VEGF both synthesis and/or activity block in clinical conditions.

Conclusions

1. The data obtained confirm the development of diabetic retinopathy in conditions of streptozotocin model of diabetes mellitus.

2. Diabetic retinopathy development characterized by vascular endothelial growth factor content in rats blood increase with the top level of increase on the 180^{th} day of the trials.

3. Aflibercept positively impacted rats' blood vascular endothelial growth factor level normalization. A more definite corrective effect was observed in its combination with L-arginine administration.

4. The prominent positive effect of VEGF level normalization was observed in the case of aflibercept, L-arginine and citicoline combined administration.

5. The pathogenetic role of immune mechanisms and their involvement in diabetic retinopathy was shown.

6. Determination of VEGF principal pathogenetic role in diabetic retinal tissue damage opened a new direction of diabetic retinopathy targeted pathogenetically determined pharmacocorrection by blocking the VEGF signaling pathway.

7. The established immune mechanisms involvement into DR pathogenetic mechanisms by blood VEGF level increase is an experimental background of reasonability of VEGF both synthesis and/or activity block in clinical conditions.

Prospects for further research aimed prospective experimental testing of diabetic retinopathy pathogenetic pharmacological correction aiming to reveal new pathogenetic launches and to increase the therapy efficacy with the perspectives of the original scheme diabetic retinopathy pathogenetic pharmacological correction use in clinical conditions.

References

1. Vastyanov RS, Stoyanov OM, Oleksyuk-Nekhames AH, Kalashnikov VY, Bakumenko IK, Gruzevskyi OA. et al. Kliniko-eksperymentalne obgruntuvannya patohenetychnoho likuvannya diabetychnoho urazhennya peryferychnoyi nervovoyi systemy. Medical Science of Ukraine. 2024; 20(2): 79 – 89. [In Ukrainian]. doi: https://doi.org/10.32345/2664-4738.2.2024.10.
2. Arrigo A, Aragona E, Bandello F. VEGF-targeting drugs for the treatment of retinal neovascularization in diabetic retinopathy. Ann Med. 2022; 54(1): 1089 – 1111. doi: 10.1080/07853890.2022.2064541.
3. Forrester JV, Kuffova L, Delibegovic M. The Role of Inflammation in Diabetic Retinopathy. Front Immunol. 2020; 11: 583687. doi: 10.3389/fimmu.2020.583687.
4. Forzano I, Avvisato R, Varzideh F, Jankauskas SS, Cioppa A, Mone P. et al. L-Arginine in diabetes: clinical and preclinical evidence. Cardiovascular Diabetology. 2023; 22: 89. doi: 10.1186/s12933-023-01827-2
5. Ghamdi AHA. Clinical Predictors of Diabetic Retinopathy Progression; A Systematic Review. Curr Diabetes Rev. 2020; 16(3): 242-247. doi: 10.2174/1573399815666190215120435.
6. Kang Q, Yang C. Oxidative stress and diabetic retinopathy: Molecular mechanisms, pathogenetic role and therapeutic implications. Redox Biol. 2020; 37: 101799. doi: 10.1016/j.redox.2020.101799.
7. Kaštelan S, Orešković I, Bišćan F, Kaštelan H, Gverović Antunica A. Inflammatory and angiogenic biomarkers in diabetic retinopathy. Biochem Med (Zagreb). 2020; 30(3): 030502. doi: 10.11613/BM.2020.030502.
8. Lin KY, Hsih WH, Lin YB, Wen CY, Chang TJ. Update in the epidemiology, risk factors, screening, and treatment of diabetic retinopathy. J Diabetes Investig. 2021; 12(8): 1322 – 1325. doi: 10.1111/jdi.13480.
9. Niklander S, Bordagaray MJ, Fernández A, Hernández M. Vascular Endothelial Growth Factor: A Translational View in Oral Non-Communicable Diseases. Biomolecules. 2021; 11(1): 85. doi: 10.3390/biom11010085.
10. Pérez-Gutiérrez L, Ferrara N. Biology and therapeutic targeting of vascular endothelial growth factor A. Nat Rev Mol Cell Biol. 2023; 24(11): 816 – 834. doi: 10.1038/s41580-023-00631-w.
11. Spencer BG, Estevez JJ, Liu E, Craig JE, Finnie JW. Pericytes, inflammation, and diabetic retinopathy. Inflammopharmacology. 2020; 28(3): 697 – 709. doi: 10.1007/s10787-019-00647-9.
12. Tan TE, Wong TY. Diabetic retinopathy: Looking forward to 2030. Front Endocrinol (Lausanne). 2023; 13: 1077669. doi: 10.3389/fendo.2022.1077669.
13. Vastyanov RS, Sadovyi OS, Stoyanov OM, Dobrovolskyi VV, Vastyanova OV, Gruzevskyi OA. Cognitive disorders expression and their pathogenetic correction in the dynamics of streptozotocin-induced diabetes. World of Medicine and Biology. 2021; 4(78): 203 – 208. doi: 10.26724/2079-8334-2021-4-78-203-208.
14. Yang J, Liu Z. Mechanistic Pathogenesis of Endothelial Dysfunction in Diabetic Nephropathy and Retinopathy. Front Endocrinol (Lausanne). 2022; 13: 816400. doi: 10.3389/fendo.2022.816400.
15. Yue T, Shi Y, Luo S, Weng J, Wu Y, Zheng X. The role of inflammation in immune system of diabetic retinopathy: Molecular mechanisms, pathogenetic role and therapeutic implications. Front Immunol. 2022; 13: 1055087. doi: 10.3389/fimmu.2022.1055087.

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