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RESEARCH OF CHANGES IN THE LEVEL OF ENDOTHELIN-1 IN EXPERIMENTAL DIABETIC RETINOPATHY. COMPARISON OF METHODS OF CORRECTION

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Abstract

Diabetic retinopathy (DR) according to the WHO is the main cause of decreased vision and blindness due to diabetes.

The aim of the study: to compare the effectiveness of correction of vasoconstriction in experimental diabetic retinopathy under the influence of different methods of correction.

Our results indicate a violation of the functional state of blood vessels on the 30th day of experimental diabetic retinopathy with subsequent progression of pathological changes on the 60th and 180th day of the study, as evidenced by a significant increase in endothelin-1 in the 2nd group ($p < 0.001$), most pronounced in the 3rd stage.In the analysis of data of group №3 it was found that the correction of pathological conditions with hypoglycemic agents has a positive effect, but does not allow to significantly correct pathologically increased levels of endothelin-1, which indicates the need for additional correction tools other than hyperglycemia.The results of group 4 indicate that the involvement of a donor of nitric oxide and aflibercept in the correction of diabetic retinopathy corrects the level of the studied

marker, the most pronounced effect is observed on the 180th day of the experiment, but normative values can not be achieved. It was found that in the 5th group, in which the correction of the simulated pathological condition was performed by reducing hyperglycemia, the introduction of aflibercept and bromfenac gives positive results, but less pronounced than in the 4th group, where L-arginine solution was added to the complex correction. .It was found that rats of group 6, which simulated diabetic retinopathy with subsequent correction of hyperglycemia, administration of aflibercept, L-carnitine and bromfenac have a pronounced effectiveness of the proposed method of correction compared to previous methods, the level of vasoconstriction stage and continues to recover in the following stages of the experiment, but does not reach the normative values. The obtained data suggest that the method of correction selected in group 7, which includes reduction of hyperglycemia, administration of aflibercept, solution of L-arginine and citicoline is most effective for normalizing vascular tone and structural and functional state of the endothelium.

Key words: experimental diabetic retinopathy; endothelial dysfunction; endothelin-1; vasoconstriction; correction.

Introduction. Diabetic retinopathy (DR) according to the WHO is the main cause of decreased vision and blindness due to diabetes. This pathology is the main cause of visual disability in the population of economically developed countries [1-4] and this is diagnosed in 40-85% of patients with diabetes.

It should be noted that even with the compensation of carbohydrate metabolism, the development of DR continues. [5-9]. To date, the key role of endothelial dysfunction in the occurrence and progression of DR has been proven [10, 11]. It has been proven that endotheliocytes are the first which suffer from hyperglycemia, glucose toxicity and dyslipidemia and under its influence begin to synthesize atherogenic factors [10, 14]. There is an increase in the permeability of the vessel wall and violation of their elasticity, which leads to hemorrhages and exudates. Transcapillary transport is disrupted, which in turn leads to retinal ischemia [14]. Under pathological conditions, there is a significant increase in the amount of endothelin-1, which in interaction with B-receptors causes a vasospastic effect [15, 16].

Hypercholesterolemia, low-density lipoprotein, hypoxia, hyperglycemia, angiotensin-2, cortisol, and thrombin also stimulate endothelin-1 expression [17]. Endothelin-1 stimulating receptors of smooth muscle cells leads to persistent vasoconstriction and

proliferation of the middle membranes of small diameter vessels. It should be noted that endothelin-1 is 100 times more potent than angiotensin-2 and during its introduction there is a reduction in coronary blood flow by 90% [15, 18]. Through the activation of cytokines, endothelin-1 enhances the inflammatory process, as well as the synthesis and secretion of factors such as fibroblast growth factor, which through the formation of extracellular matrix causes the development of vascular pathology [15, 17-20, 26, 27]. During the development of endothelial dysfunction endothelin01 doesn't only take an active part in this process, but can also lead to insulin resistance due to an increase in the amount of reactive oxygen species, especially superoxidation.

It should be noted that closely related to active forms of oxygen E-1 indirectly initiates cardiovascular dysfunction and diabetic complications [21]. Given the above, it is important to find new ways of correction that will not have only a hypoglycemic effect, but will improve the condition of blood vessels in diabetes, correct pathological vasoconstriction and prevent the rapid development of proliferative diabetic retinopathy.

The aim of the study: to compare the effectiveness of correction of vasoconstriction in experimental diabetic retinopathy under the influence of different methods of correction.

Materials and methods. The study was performed on white Wistar rats weighing 180-200 g. According to the tasks, the animals were divided into 7 groups:

Group 1 - 60 intact animals;

Group 2 - 60 animals in which diabetic retinopathy was simulated without further correction.

Group 3 - 60 animals in which diabetic retinopathy was simulated with subsequent correction of hyperglycemia.

Group 4 - 60 animals in which diabetic retinopathy was simulated with subsequent correction of hyperglycemia, administration of aflibercept and L-arginine solution.

Group 5 - 60 animals in which diabetic retinopathy was simulated with subsequent correction of hyperglycemia, administration of aflibercept and bromfenac.

Group 6 - 60 animals in which diabetic retinopathy was simulated with subsequent correction of hyperglycemia, administration of aflibercept, L-carnitine and bromfenac.

Group 7 - 60 animals in which diabetic retinopathy was simulated with subsequent correction of hyperglycemia, administration of aflibercept, L-arginine solution and citicoline.

Type 2 diabetes mellitus and diabetic retinopathy were modeled by intraperitoneal administration of streptozotocin (Sigma, USA) dissolved in 0.1 M citrate buffer with pH 4.5

[22]. The dose of streptozotocin 55 mg / kg animal weight was divided into two injections. The administration of streptozotocin was preceded by a high-fat diet for 28 days [23].

Doses of drugs: Hypoglycemic drug - metformin (Merck Sante, manufactured in France) - at a dose of 300 mg / kg body weight in drinking form in 0.9% sodium chloride solution through a syringe with an intragastric tube daily. Administration of L-arginine solution, which is a donor of NO, (SIMESTA, made in China, USP32 quality standard) was carried out by intragastric administration of L-arginine solution in 0.9% sodium chloride solution at a dose of 500 mg / kg through a syringe with an intragastric tube. The volume of the solution depended on the weight of the animal and did not exceed 1 ml. The drug was administered once a day before morning feeding, daily for 10 days. Aflibercept (anti-VEGF therapy) was administered as a subconjunctival injection at a dose of 0.08 ml (25 mg / ml). Bromfenac - instillation of 0.09% eye drops once a day. L-carnitine (Sigma, USA) was administered in the form of an aqueous solution through a syringe with an intragastric tube at a dose of 25 mg / 100 g of animal weight. Citicoline - 81.8 mg / kg (0.33 ml / kg) was administered intramuscularly once a day.

Administration of L-arginine solution, which is a donor of NO, (SIMESTA, made in China, USP32 quality standard) was carried out by intragastric administration of L-arginine solution in 0.9% sodium chloride solution at a dose of 500 mg / kg through a syringe with an intragastric tube. The volume of the solution depended on the weight of the animal and did not exceed 1 ml. The drug was administered once a day before morning feeding, daily for 10 days. Aflibercept (anti-VEGF therapy) was administered as a subconjunctival injection at a dose of 0.08 ml (25 mg / ml). Bromfenac - instillation of 0.09% eye drops once a day. L-carnitine (Sigma, USA) was administered in the form of an aqueous solution through a syringe with an intragastric tube at a dose of 25 mg / 100 g of animal weight. Citicoline - 81.8 mg / kg (0.33 ml / kg) was administered intramuscularly once a day.

Withdrawal of animals from the experiment was carried out in three stages: 1st stage of the study - the 30th day after the start of modeling diabetes; 2nd stage of the study - the 60th day after the start of modeling diabetes; Stage 3 of the study - the 180th day after the start of modeling diabetes.

Animals were removed from the experiment by decapitation under light ether anesthesia in accordance with the "Rules of work with experimental animals", approved by the Order of the Ministry of Health of Ukraine № 249 from 01.03.2012 and the Law of Ukraine № 3447-IV "On protection of animals from cruelty" from 15.12.2009 and from

16.10.2012). Blood was taken from the retroorbital venous plexus, which lies in orbit behind the eyeball. (A.V.Dyakonov, I.S.Khrikina, A.A.Hegai and others, 2013).

Statistical processing of the obtained results. To detect changes in the studied indicators between different groups and at different stages, we used parametric statistical methods, which are based on the operation with the parameters of statistical distribution (mean and variance). The used methods are designed for normally distributed data, so we checked all the data for normality using the criterion of asymmetry and excess E.I. Pustylnyk. All the data we consider were normally distributed, so you can compare the average values of the samples in pairs. Note that in subsequent comparisons, we perform comparisons in independent samples. These will be comparisons between different groups of animals or comparisons between the same group of animals (but since there is no correspondence between animals in the samples, they will also be independent). A value of $p < 0.05$ was chosen as the criterion of reliability. An analysis was made as to whether the mean values differed. The results of determining the t-criterion give an answer about the equality or difference of the mean values, but they do not allow to accurately measure the difference between the mean values. Note that this difference is quite conditional. This difference was calculated as a percentage. Thus, we demonstrated a comparison of the mean values between different groups of animals.

The results of the study and their discussion:

Endothelin-1 is considered a classic vasoconstrictor, which during experiments also detects mitogenic functions. There is a close correlation between the rate of endothelial dysfunction and the concentration of endothelin-1 in blood plasma. A number of researchers also noted high levels of endothelin in experimental animals during simulated hypercholesterolemia. The same trend was observed in patients with hypercholesterolemia. In cardiovascular pathology, in particular unstable angina or acute myocardial infarction, patients also had an increased concentration of this indicator in blood plasma [24, 25].

The results of the study of this indicator in experimental diabetes mellitus and diabetic retinopathy are presented in Table 1.

In the group №2, in which the pathological process was simulated without further correction at the first stage, a significant increase in the studied indicator was found in comparison with the data of intact animals. In the second value of this indicator increased statistically significantly compared to the results of the same group in the previous stage. In the third stage, data were obtained indicating the progression of structural and functional

disorders of the endothelium and an increase in pathological vasoconstriction against the background of the development of experimental diabetic retinopathy.

Table 1 - The level of endothelin-1 in the blood of experimental animals with simulated diabetic retinopathy and with different methods of its correction on the 30th, 60th and 180th day (M ± m), (pkg / l).

Stages / Groups	I stage	II stage	III stage
1 group	3,03±0,18	3,03±0,16	3,03±0,18
2 group	7,02±0,22	8,05±0,2	8,34±0,2
3 group	5,31±0,21	5,9±0,2	6,42±0,18
4 group	5,18±0,15	5±0,19	4,93±0,18
5 group	5,04±0,18	5,16±0,2	5,21±0,2
6 group	4±0,21	3,84±0,21	3,64±0,2
7 group	4,12±0,16	3,58±0,16	3,11±0,13

Consider in more detail the impact of corrective measures. Thus, in the third group, whose animals received metformin on the background of the simulated pathological condition, the following data were obtained. At the first stage, the level of the studied marker is 42.92% ($p < 0.001$) higher than the value of intact animals. Compared with group №2, its level is lower by 32.14% ($p < 0.001$). In the second stage, the E1 content is 9.88% ($p < 0.05$) higher than in the previous stage. Compared to the group of intact animals, it is higher by 48.56% ($p < 0.001$), and compared to the group without correction lower by 36.69% ($p < 0.001$). In the third stage, the level of this marker pathologically increased by 17.27% ($p < 0.001$) compared to the 1st stage and by 8.2% ($p < 0.05$) compared to the 2nd. This suggests that the correction of hyperglycemia alone is not enough to normalize vascular tone in experimental diabetic retinopathy and vasoconstriction is steadily progressing. Compared to the first group, the value of E1 is higher by 52.74% ($p < 0.001$), and relative to the second - lower by 29.97% ($p < 0.001$).

In group №4, in which diabetic retinopathy was corrected by correction of hyperglycemia, administration of aflibercept and L-arginine solution, the level of endothelin-1

in the first stage is higher by 41.48% ($p < 0.001$) compared with the intact group, relative to the 2nd group, it is less pronounced by 35.47% ($p < 0.001$). No statistically significant differences were found compared to group №3. In the second stage, the content of E1 is 39.37% ($p < 0.001$) compared to the intact group, compared to group №2 it is lower by 61.10% ($p < 0.001$), and compared to the 3rd lower by 17, 86% ($p < 0.001$). At the third stage, the level of the studied marker is 38.48% ($p < 0.001$) higher than the group №1. Compared to group №2, it is lower by 69.19% ($p < 0.001$), and compared to group 3 - by 30.18% ($p < 0.001$).

In the fifth group, the correction of pathology was carried out by the introduction of metformin, aflibercept and bromfenac, the following results were obtained. In the blood of animals in the first stage, the level of E1 is increased by 39.87% ($p < 0.001$) compared to these intact rats, compared with group №2 it is lower by 39.20% ($p < 0.001$). No statistically significant differences were found in comparison with groups №3 and №4. In the second stage, the content of endothelin-1 by 41.22% ($p < 0.001$) is higher compared to group 1, lower than the 2nd group of rats by 56.18% ($p < 0.001$) and 14.26% (0.001) relative to the 3rd group. No statistically significant differences were found compared with group №4. In the third stage, the values of the studied marker are higher by 41.75% ($p < 0.001$) relative to the intact group. Compared with group №2, the level was lower by 60.20% ($p < 0.001$), compared with group №3 - by 23.26% ($p < 0.001$). Differences in comparison with group №4 are not established.

In group №6, simulated diabetic retinopathy was corrected with metformin, aflibercept, L-carnitine, and bromfenac. At the first stage in this group the level of vasoconstriction is higher by 24.29% ($p < 0.001$) compared to the 1st group. For all the following groups it is lower: compared to the 2nd - by 75.26% ($p < 0.001$), compared to the 3rd by 32.63% ($p < 0.001$), relative to the 4th group of animals - by 29, 37% ($p < 0.001$) and relative to the 5th by 25.91% ($p < 0.001$). At stage №2 (60th day of the experiment) the level of E1 is higher by 21.24% ($p < 0.01$) compared to the first group. In comparison with group №2 it is lower by 109.26% ($p < 0.001$), in comparison with the 3rd - by 53.09% ($p < 0.001$), in comparison with the 4th group it is lower by 29.9% (0.001) and relative to the 5th lower by 33.99% ($p < 0.001$). At the third stage, the content of the indicator is 16.66% ($p < 0.05$) higher than the norm, 129.22% ($p < 0.001$) lower compared to the data of group №2. The increase is much less pronounced for all groups with correction: relative to the 3rd by 76.36% ($p < 0.001$), relative to the 4th by 35.48% ($p < 0.001$), and relative to the 5th - by 43.08 % ($p < 0.001$).

In the seventh group, the simulated pathological process was corrected by the introduction of metformin, aflibercept, L-arginine solution and citicoline. Obtained cumulative results: the level of Endothelin-1 by 26.49% ($p < 0.001$) is higher relative to the intact group in the 1st stage. Compared to the 2nd group, it is lower by 70.18% ($p < 0.001$), compared to the 3rd - by 28.78% ($p < 0.001$), relative to the 4th - by 25.62% ($p < 0.001$), and relative to the 5th by 22.26% ($p < 0.001$). No statistically significant differences compared to group №6 were found at this stage. In the second stage, the level of the marker is 15.22% ($p < 0.05$) lower than the previous one. Compared to the first group, it is higher by 15.3% ($p < 0.01$). Compared to the 2nd - lower by 125.06% ($p < 0.001$), compared to the 3rd - by 64.65% ($p < 0.001$), compared to the 4th and 5th groups lower by 39.7% ($p < 0.001$) and 44.1% ($p < 0.001$), respectively. Compared with the sixth group, the differences are not statistically established. In the third stage, the level of the indicator is lower by 32.62% ($p < 0.001$) compared to the 1st stage and by 15.1% ($p < 0.05$) compared to the 2nd. It is noteworthy that there are no differences between the data of intact animals and the 7th group, which indicates the normalization of endothelin-1 levels in the blood of rats. Compared to the 2nd group, the result is better by 168.3% ($p < 0.001$), relative to the 3rd - by 106.43% ($p < 0.001$), compared to the 4th - by 58.58% ($p < 0.001$)), compared to the 5th by 67.48% ($p < 0.001$), relative to the 6th group showed an improvement of 17.05% ($p < 0.05$).

The obtained data indicate the normalization of vascular tone in rats of the 6th and 7th groups, more pronounced improvement is observed in the seventh group (Dynamics of the level of the indicator is clearly illustrated in Figure 1.)

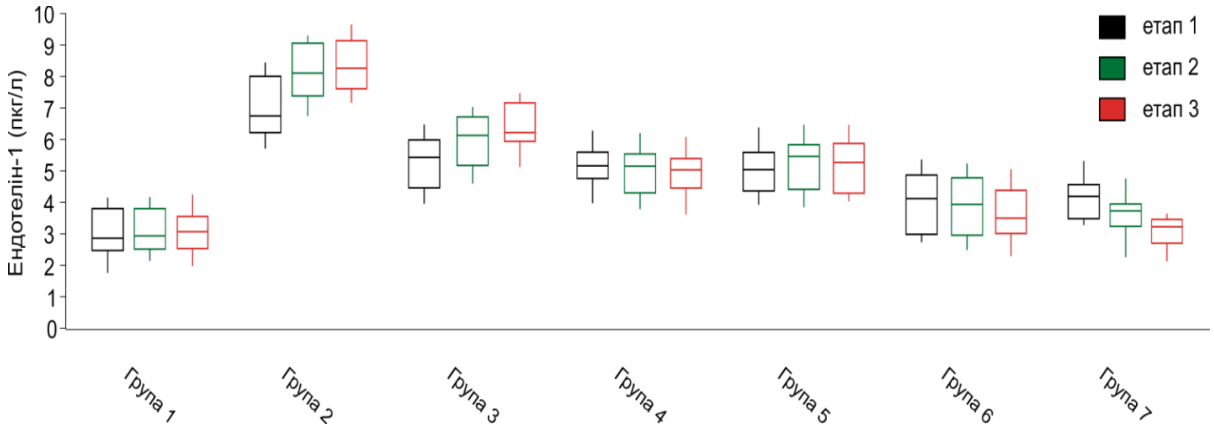

Figure 1 - The level of endothelin-1 in the blood of experimental animals with simulated diabetic retinopathy and with different methods of its correction on the 30th, 60th and 180th day. Box rafts illustrate the distribution of the values of the level of the studied indicator in all groups of the experiment at each stage of the study (n = 20).

Conclusions:

1. Our results indicate a violation of the functional state of blood vessels on the 30th day of experimental diabetic retinopathy with subsequent progression of pathological changes on the 60th and 180th day of the study, as evidenced by a significant increase in endothelin-1 in the 2nd group ($p < 0.001$), most pronounced in the 3rd stage.

2. In the analysis of data of group №3 it was found that the correction of pathological conditions with hypoglycemic agents has a positive effect, but does not allow to significantly correct pathologically increased levels of endothelin-1, which indicates the need for additional correction tools other than hyperglycemia.

3. The results of group 4 indicate that the involvement of a donor of nitric oxide and aflibercept in the correction of diabetic retinopathy corrects the level of the studied marker, the most pronounced effect is observed on the 180th day of the experiment, but normative values can not be achieved.

4. It was found that in the 5th group, in which the correction of the simulated pathological condition was performed by reducing hyperglycemia, the introduction of aflibercept and bromfenac gives positive results, but less pronounced than in the 4th group, where L-arginine solution was added to the complex correction.

5. It was found that rats of group 6, which simulated diabetic retinopathy with subsequent correction of hyperglycemia, administration of aflibercept, L-carnitine and bromfenac have a pronounced effectiveness of the proposed method of correction compared to previous methods, the level of vasoconstriction stage and continues to recover in the following stages of the experiment, but does not reach the normative values.
6. The obtained data suggest that the method of correction selected in group 7, which includes reduction of hyperglycemia, administration of aflibercept, solution of L-arginine and citicoline is most effective for normalizing vascular tone and structural and functional state of the endothelium.

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