Experimental Studies

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Relationships between structural changes, marker of apoptosis and metabolic parameters in the retina of rats with diabetes and myopia

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Purpose: *To examine the relationships among retinal structural changes, apoptosis marker, and retinal metabolic parameters in animals with experimental diabetes and high myopia.*

Material and Methods: *Fifty-five Wistar rats (age, 2 weeks) were used in experiments. High myopia was produced in animals by surgically fusing the eyelids of both eyes. In some rats with myopia, diabetes was induced by streptozotocin injection (a subdiabetic dose of 15 mg/kg body weight, intraperitoneally for 5 days). Rats were assigned to four groups: group 1 (myopia alone), group 2 (diabetes alone), group 3 (both myopia and diabetes), and group 4 (healthy controls). In two months, histomorphological studies were conducted, and the number of retinal ganglion cells (RGCs) was determined in the field of view. The clinical status of the retina was assessed by ophthalmoscopy. Retinal fragmented DNA (fDNA) level was determined by spectrophotometry. Statistical analysis was used to examine the relationships between retinal structural and metabolic changes. Parametric (Student t-test) and non-parametric tests (Mann-Whitney U test, Kruskal-Wallis test and Spearman rank correlation analysis) were employed.*

Results: *Morphometric studies demonstrated that the number of RGCs was substantially reduced in diabetic animals compared to controls, and increased in diabetic animals with myopia compared to animals with diabetes alone. Retinal fDNA level was increased in diabetic animals compared to controls, and reduced in diabetic animals with myopia compared to animals with diabetes alone. There was a negative correlation between the number of RGCs and retinal fDNA level for animals with diabetes alone and diabetic animals with myopia. A positive correlation was found between the number of RGCs and retinal metabolic parameters.*

Conclusion: *Myopization can prevent the development of retinal diabetic complications. Retinal energy processes, brain-derived neurotrophic factor and low early apoptosis of RGCs are involved in the regulation of protection from diabetic retinopathy.*

Keywords:

diabetic retinopathy, myopia, rats, retina, metabolism, apoptosis, structural changes, ganglion cells

Introduction

Diabetic retinopathy (DR) is still a leading cause of vision loss among working-age adults and thus a major medical and social challenge. By 2045, the number of adults worldwide with vision-threatening DR (VTDR) is projected to increase to 44.82 million [1, 2].

Hyperglycemia, oxidative stress, endothelial dysfunction and retinal neurodegeneration are implicated in the pathogenesis of DR with the development of metabolic abnormalities in the eye [3-5].

Measurements indicating retinal ganglion cell (RGC) loss and inner retinal layer thinning support early neurodegeneration in diabetes [6].

Although there have been numerous publications on the pathogenesis of DR associated with other diseases, the problem is still unresolved. Paradoxically, myopic diabetics hardly ever develop severe DR and do not develop proliferative DR [7,8].

Various models of hyperglycemic type I diabetes (T1DM) and type 2 diabetes (T2DM) [9] and diabetes in the presence of high myopia [10] have been developed. Because DR is a multifactorial disease with genetic, environmental, vascular, and neurological factors, application of models of diabetes with concomitant diseases is important for the investigation of pathophysiological and molecular mechanisms of DR [9].

Although most diabetics have T2DM, it should be mentioned that the retinal histology of T2DM animals showed a surprising similarity to T1DM animals indicating that despite the different evolution of the disease, the neuroretinal cells affected are the same in both subtypes of diabetes [11]. No study has, however, investigated the hystomorphological and immunochemical changes in animal neuroretinal cells in T2DM in the presence of axial myopia.

In recent decades, special attention has been given to research on the molecular mechanisms of degenerative ocular disorders, especially DR (including DR in the presence of myopia), aiming to develop pathogenetic treatment strategies to be used in the clinical setting [12-15]. Therefore, experimental studies on adequate disease models which contribute to the elucidation of the mechanisms are relevant.

The purpose of the study was to examine the relationships among retinal structural changes, apoptosis marker, and retinal metabolic parameters in animals with experimental diabetes plus high myopia.

Material and Methods

All animal experiments were performed in compliance with the provisions of the European Convention on the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 1986) and Guidelines for Works Involving Experimental Animals approved by the Law of Ukraine on the Protection of Animals from Cruelty (No. 1759-VI dated December 15, 2009) and decision of the local bioethics committee.

Fifty-five Wistar rats (age, 2 weeks) were used in experiments. They were assigned to four groups: group 1 (myopia alone, 15 animals, 30 eyes), group 2 (diabetes alone, 15 animals, 30 eyes), group 3 (both myopia and diabetes, 15 animals, 30 eyes), and group 4 (healthy controls, 10 animals, 20 eyes). High form-deprivation myopia was produced in animals by surgically fusing the eyelids of both eyes [10]. In rats in groups 2 and 3, diabetes was induced by streptozotocin (STZ) injection (a subdiabetic dose of 15 mg/kg body weight, intraperitoneally for 5 days) for the development of moderate hyperglycemia and to reduce the possibility of animal death [10]. STZ injection for 5 days caused the development of diabetic changes in the rat retina. Blood glucose was measured with the IME-DC glucose meter (Germany) for the diagnosis of diabetes. A glucose level of at least 4.5 mmol/L was a criterion of the development of diabetes. The state of the retina was assessed by ophthalmoscopy.

In two months, all rats were sacrificed under anesthesia. Retinal sections were stained with hematoxylin and eosin. Thereafter, microscopy was performed and images were collected and evaluated on a light microscope Jenamed 2 (Carl Zeiss Jena, Jena, Germany). Morphometry of the number of RGCs was determined in the field of view. Fragmented DNA (fDNA) level in the rat retina was determined by spectrophotometry [16].

Correlation was assessed between the number of RGCs in the field of view and fDNA level. In addition, correlations were assessed between retinal histological parameters and previously determined metabolic parameters (namely, the retinal brain-derived neurotrophic factor (BDNF) concentration and retinal energy metabolism parameters) [13,14].

Numbers of RGCs were processed using non-parametric tests (namely, Mann-Whitney U test and Kruskal-Wallis test). Differences between groups in biochemical parameters were analyzed with a parametric Student's t-test when normally distributed. Biochemical parameter data are presented as mean and error of mean. Numbers of RGCs were non-normally distributed and described using median (Med) and interquartile range (IQR). Relationships between retinal structural changes and metabolic parameters were tested using the non-parametric Spearman rank correlation coefficient.

Results

Rat blood glucose levels were tested for glycemia when modeling diabetes. Moderate hyperglycemia was noted, with a 78.1% increase in the blood glucose level ($p < 0.001$) compared to controls, after the rats in group 2 received the subdiabetic dose of STZ for five days. In the group with both myopia and diabetes, the blood glucose level was found to be increased by 81.6% ($p < 0.001$) compared to controls (Table 1).

The next phase of the study was determining the level of fDNA (a marker of early apoptosis) in the retina (Table 2). The mean retinal fDNA level was 42.5% and 33.4% higher in the group with both myopia and diabetes than in the control group and the myopia-alone group, respectively. Although there was no significant difference in the retinal fDNA level between the group with both myopia and diabetes and the group with diabetes alone, there was a clear tendency towards a reduced retinal fDNA level in the former group, likely due to substantial variations in the values of this parameter in the groups. In the group with diabetes alone, the retinal fDNA level was found to be increased by 56.8% compared to the control group ($p < 0.01$), and by 46.8% compared to the group with myopia alone ($p < 0.05$).

Two months after modeling diabetes and myopia, we conducted a morphometric study to estimate numbers of RGCs in the field of view (Table 3). The numbers of RGCs in the field of view in the group with myopia alone and the group with diabetes alone were found to be 20.0% and 64.4% lower, respectively, than in the control group. In the group with both myopia and diabetes, however, the numbers of RGC in the field of view were just 28.9% lower than in the control group, and 100% higher than in the diabetes alone group.

The next phase of the study was examining the relationships among retinal structural and metabolic parameters in different groups of experimental animals (Table 4). We found a negative correlation between the number of RGCs in the field of view and retinal fDNA level

Table 1. Blood glucose levels in rats with myopia alone, diabetes alone and both myopia and diabetes and controls

Statistics	Groups of animals			
	Control group (n = 10)	Myopia alone (n = 15)	Diabetes alone (n = 15)	Both myopia and diabetes (n = 15)
M±m	2.78±0.14	2.93±0.15	4.95±0.32	5.05±0.20
%	100.0	105.4	178.1	181.6
p	-	>0.05	<0.001	<0.001
$\%_1$	-	100.0	168.9	172.4
p_1	-	-	<0.001	<0.001
$\%_2$	-	-	100.0	102.0
p_2	-	-	-	>0.05

Note: n, number of animals; p, significance of difference compared to control; p_1, significance of difference compared to myopia alone; p_2, significance of difference compared to diabetes alone; M, mean value; m, standard error of mean

Table 2. Retinal fDNA levels in rats with myopia alone, diabetes alone and both myopia and diabetes and controls

Statistics	Groups of animals			
	Control group (n = 10)	Myopia alone (n = 15)	Diabetes alone (n = 15)	Both myopia and diabetes (n = 15)
M±m	9.14±0.82	9.76±0.92	14.33±1.45	13.02±1.34
%	100.0	106.8	156.8	142.5
p	-	>0.05	<0.01	<0.05
$\%_1$	-	100.0	146.8	133.4
p_1	-	-	<0.05	>0.05
$\%_2$	-	-	100.0	90.9
p_2	-	-	-	>0.05

Note: n, number of animals; p, significance of difference compared to control; p_1, significance of difference compared to myopia alone; p_2, significance of difference compared to diabetes alone; M, mean value; m, standard error of mean

for rats with diabetes alone (R=–0.74, $p < 0.05$) and diabetic myopic rats (R = –0.72, $p < 0.05$); that is, neuroretinal cell damage was less pronounced in a portion of animals with high myopia. This indicates the informativeness of fDNA (a marker of early apoptosis) in predicting diabetic changes in the retina. For hyperglycemic rats without myopia, we found positive correlations between the number of RGCs in the field of view and retinal levels of BDNF (R = 0.52, $p < 0.05$), adenosine triphosphate (ATP) (R = 0.52, $p < 0.05$), adenosine diphosphate (ADP) (R = 0.53, $p < 0.05$), and succinate dehydrotase (SDH) activity (R = 0.56, $p < 0.05$), and negative correlations between the number of RGCs in the field of view and retinal levels of lactate and pyruvate (R = –0.54 and R = –0.51, respectively, $p < 0.05$). For hyperglycemic rats with myopia, we found positive correlations between the number of RGCs in the field of view and retinal levels of BDNF (R = 0.58, $p < 0.05$), ATP (R = 0.67, $p < 0.05$), ADP (R = 0.64, $p < 0.05$), and SDH activity (R = 0.62, $p < 0.05$) and negative correlations between the number of RGCs in the field of view and retinal levels of lactate and pyruvate (R = –0.56 and R = –0.54, respectively, $p < 0.05$).

Table 3. Numbers of retinal ganglion cells in the field of view in rats with myopia alone, diabetes alone and both myopia and diabetes and controls

Statistics	Groups of animals			
	Control group (n = 10)	Myopia alone (n = 15)	Diabetes alone (n = 15)	Both myopia and diabetes (n = 15)
Медіана	22.5	18	8	16
Q_{low} - Q_{up}	19.0-26.0	15.0-22.0	6.0-12.0	13.0-20.0
%	100.0	80.0	35.6	71.1
p	-	>0.05	<0.001	<0.001
$\%_1$	-	100.0	44.4	88.9
p_1	-	-	<0.001	>0.05
$\%_2$	-	-	100.0	200.0
p_2	-	-	-	<0.01

Note: n, number of animals; p, significance of difference compared to control; p_1, significance of difference compared to myopia alone; p_2, significance of difference compared to diabetes alone; M, mean value; m, standard error of mean

These findings indicate that the investigated metabolic changes are involved in the protective effect of eye myopization in retinal diabetic changes in experimental animals. Further research is, however, warranted to elucidate exact mechanisms of the positive effect of myopization on the retinal structure and metabolism in diabetes.

Discussion

Today, the exact mechanism of the protective effect of myopization on the potential risk of DR progression remains unresolved. Different factors are being considered for this phenomenon. In addition, there have been contradictory reports regarding the protective effect of myopia [17]. Lim and colleagues concluded that myopia and diabetes are important factors affecting peripapillary retinal nerve fiber layer (pRNFL) thickness, and the simultaneous presence of diabetes and myopia results in greater pRNFL damage than observed with either pathology alone. Kim and colleagues [19] performed linear regression analysis to identify factors associated with ganglion cell complex

Table 4. Pairs of correlations between examined parameters for rats with diabetes alone and rates with both myopia and diabetes

Pairs of correlations		Examined groups of animals			
		Diabetes alone		Both myopia and diabetes	
		Correlation coefficient	P-value	Correlation coefficient	P-value
Number of RGCs	fDNA	-0.74	< 0.05	-0.72	< 0.05
Number of RGCs	SDH	0.56	< 0.05	0.62	< 0.05
Number of RGCs	ATP	0.58	< 0.05	0.67	< 0.05
Number of RGCs	ADP	0.53	< 0.05	0.64	< 0.05
Number of RGCs	BDNF	0.52	< 0.05	0.58	<0.05
Number of RGCs	Lactate	-0.54	< 0.05	-0.56	< 0.05
Number of RGCs	Pyruvate	-0.51	< 0.05	-0.54	< 0.05

(GCC) thickness and found that DM duration and axial length [AL] were significantly associated with parafoveal GCC thickness. They concluded that the combination of mechanical stretching and neurodegeneration would accelerate neural damage to the retina, resulting in greater inner retinal layer thinning.

Most publications, however, suggest that individuals with myopia exhibit a decreased risk of developing DR or VTDR [7, 20-23]. A meta-analysis was conducted to estimate the relationship between refractive error and the risk of DR in diabetics, and to assess whether VTDR is associated with refractive error. The meta-analysis demonstrated that hyperopia was associated with an increased risk of VTDR, and myopia was associated with a reduced risk of DR in diabetics [24, 25]. High-myopic refractive error was found to be protective for VTDR in type 2 DM, but not in type-1 DM [26].

A potential protective mechanism of high myopia against the potential risk of DR progression has been discussed in several works. Thus, there is an opinion that axial myopia is characterized by retinal arterioles that are longer and narrower than those in "normal" or emmetropic eyes, resulting in a lowered blood pressure and capillary hydrostatic pressure, and decreasing the tendency of the small vessels to leak and rupture in these patients [27,28].

Lin and colleagues [29] concluded that high myopia was negatively associated with both DR and non-proliferative DR, and this protective effect may have been partially achieved via thinning retinal veins [29]. The retina receives its nutrients from two separate circulations (retinal and choroidal circulations) that may be somewhat involved in the above effects, given that retinal circulation is characterized by a low blood flow while flow in the choroid is high [30].

He and colleagues [31] reported that the possible mechanisms for the protective effect of myopia against DR may include posterior vitreous detachment, change in retinal blood flow and oxygen demand, choroidal thinning and altered cytokine profiles.

Shao and Yao [32] reported that, in the eye of myopic patients with DR, transthyretin (TTR, a thyroxine and retinol transport protein) could regulate the transcription of key genes in Tie2 (a receptor tyrosine kinase on vascular endothelial cells) pathway for neovascularization, and then could affect the contents of their protein products. In addition, the results suggest that there should be a protective association between abundant TTR levels in the vitreous of highly myopic patients and a decreased risk of DR. TTR level in DR was much was much lower than that in diabetes and high myopia; the expression of TTR might be blocked by some other unknown anti-TTR mechanism. TTR might be a protective factor to decline the rate of DR in diabetes with high myopia [32].

Kim and colleagues [20] reported that axial myopia and low HbA1c level are correlated and have a suppressive effect on DR.

Kulshrestha and colleagues [33] observed significant decrease in vascular endothelial growth factor (VEGF) concentration in patients with AL ≥ 23.30 mm as compared with AL ≤ 23.30 mm in non-diabetics, diabetics without non-proliferative DR, and diabetics with non-proliferative DR. Their findings strengthened the concept that an increase in AL leads to less VEGF in diabetic eyes, thus leading to less severe DR changes [33].

In the current study, we found that the retinal fDNA level was significantly increased in animals with experimental diabetes, indicating damage to the biological eye structures. Of note that, in the current study, although there was no significant difference in the retinal fDNA level between myopic animals with diabetes and animals with diabetes alone, there was a clear tendency towards a reduced retinal fDNA level in the former animals, likely due to substantial variations in the values of this parameter in the groups. In addition, in myopic animals with diabetes, the number of RGCs in the field of view was higher than in animals with diabetes alone, and there was a statistically significant negative correlation between the number of RGCs and the retinal fDNA level; that is, neuroretinal cell damage was

less pronounced in a portion of animals with high myopia. Moreover, we found positive correlations between the number of RGCs in the field of view and retinal energy metabolism parameters (the levels of ATP and succinate dehydrotase activity) and negative correlations between the number of RGCs in the field of view and retinal levels of lactate and pyruvate, for myopic animals with diabetes. A positive correlation was found between the number of RGCs in the field of view and retinal BDNF protein level for myopic rats with diabetes. A low-level BDNF plays an important pathogenetic role in the development of neurodegeneration and retinopathy. The establishment of the above relationship may be beneficial for the diagnosis and prognosis of the development of eye disease.

Our finding of the relationships between the hystomorphological parameters, energy metabolism markers, BDNF level and fDNA (a marker of early apoptosis) in animals with diabetes induced in the presence of axial myopia may have a value for establishing the mechanism of mutual influence between myopia and diabetic retinal complications.

In conclusion, further research on the (1) systemic regulatory mechanisms and cellular metabolism mechanisms that support retinal homeostasis, (2) factors of dyshomeostasis, and (3) their relationships with biometric parameters of the eye, will contribute to the development of a DR treatment strategy based on a pathogenetic approach which would be capable of correcting detected abnormalities in the posterior eye [31,34].

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Abbreviations: *ADP, adenosine diphosphate; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; DR, diabetic retinopathy; fDNA, fragmented deoxyribonucleic acid; RGC, retinal ganglion cell; SDH, succinate dehydrotase*