Am J Transl Res 2024;16(6):2509-2516
www.ajtr.org /ISSN:1943-8141/AJTR0156144

Original Article

Effect of propylene glycol mannate sulfate on non-proliferative diabetic retinopathy

Mingming Wang[1], Bangjian Song[2], Haining Xu[3]

[1]Department of Ophthalmology, Chengyang People's Hospital, Qingdao, Shandong, China; [2]Department of Ophthalmology, Rizhao Central Hospital, Rizhao, Shandong, China; [3]Department of Ophthalmology, Weihaiwei People's Hospital, Weihai, Shandong, China

Received February 26, 2024; Accepted May 17, 2024; Epub June 15, 2024; Published June 30, 2024

Abstract: Purpose: To evaluate the effect of propylene glycol mannate sulfate (PGMS) on retinopathy in non-proliferative diabetic patients. Methods: Eighty patients (111 eyes) with non-proliferative diabetic retinopathy were selected and retrospectively analyzed. Patients were divided into a control group (40 cases, 56 eyes) and an experimental group (40 cases, 55 eyes) using a random number table method. The control group continued had routine blood glucose management, while the experimental group received PGMS 100 mg additionally TID for 60 days. Changes in visual acuity, fundus conditions including hemorrhage points and exudation in each quadrant, and non-perfusion area were revealed through fundus angiography before and after the treatment period. Results: After PGMS treatment, the experimental group demonstrated significant improvements compared to the control group in terms of eyesight improvement (P=0.002), the macular edema and macular retinal thickness (P=0.008). The total clinical efficacy rate of the experimental group was 67.86%, which was higher than 38.18% of the control group (P=0.032). Notably, there was a significant reduction in macular hemorrhage and hard extrusion. Conclusion: Oral administration of PGMS is an effective treatment for non-proliferative diabetic retinopathy.

Keywords: Propylene glycol mannate sulfate, diabetes, diabetes retinopathy, fundus angiography

Introduction

Diabetic retinopathy (DR) is a prevalent microvascular complication and the primary cause of vision loss in diabetes patients [1]. With diabetes incidence increasing, especially in emerging Asian countries like India and China [2, 3], DR is becoming a more significant public health issue. The disease can progress to severe stages like proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME). Although the specific pathogenesis of DR remains unclear, growing evidence suggests that inflammatory reactions and inflammatory factors are crucial in its development [4, 5].

Propylene glycol mannate sulfate (PGMS) is a novel, low-molecular-weight acidic polysaccharide drug developed by the Research Institute of Marine Medicine and Food of Ocean University of China. This drug is derived from polysaccharide sulfate (PSS) and belongs to the category of linear anionic polysaccharides. Previous experiments have shown that PGMS can protect vascular endothelial cells from inflammatory factors and various types of chemical damage [6]. Additionally, PGMS has been shown to reduce blood lipids and circulating inflammatory factors in diabetic patients, potentially offering protection against diabetic nephropathy [7]. While some basic studies are exploring the role of glycerides in the treatment of various disease [8-10], the therapeutic effects and mechanisms of glycerides in managing DR have yet to be documented. Therefore, we designed this experiment to explore the therapeutic effect of PGMS on non-proliferative DR.

Methods

Study population

Patients with non-proliferative DR diagnosed in the Department of Ophthalmology, Chengyang People's Hospital from March 2020 to October

https://doi.org/10.62347/URTF9525

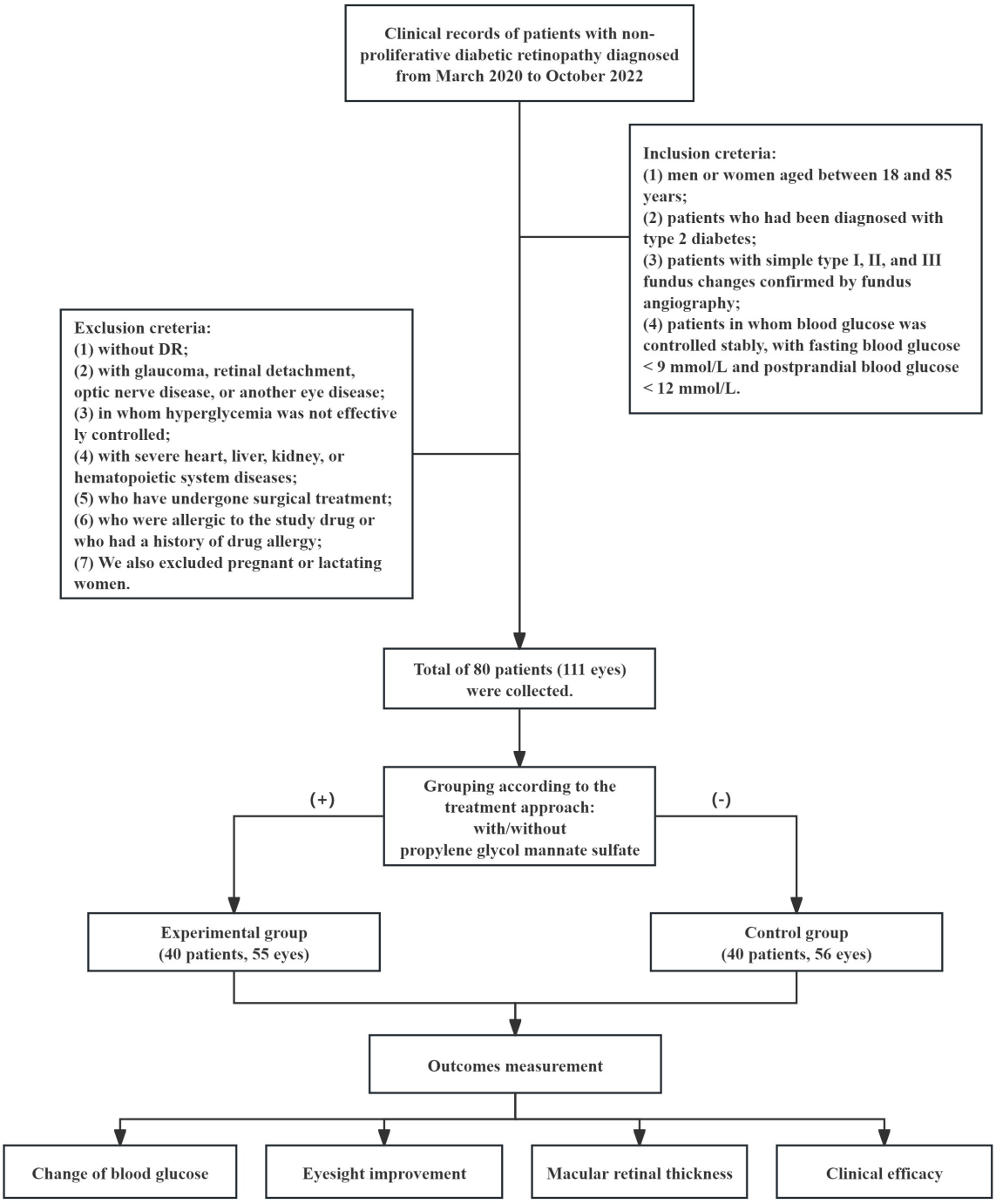

Figure 1. Flow chart of the study.

2022 were retrospectively included for this study. Diagnostic criteria were based on the Research Progress in The Diagnosis and Treatment of Diabetic Retinopathy [11]. The flow chart of the study is shown in **Figure 1**. This study was approved by the ethical committee of the Chengyang People's Hospital.

Inclusion criteria

(1) Patients with an age of 18-85; (2) Patients diagnosed with type 2 diabetes; (3) Patients with simple type I, II, and III fundus changes confirmed by fundus angiography; and (4) Patients with stable blood glucose level (fasting

Table 1. General characteristics of patients in the study groups

Item	Experience group (PGMS+)	Control group (PGMS-)	t/χ^2	P
Age, years	61.27 ± 8.53	62.25 ± 8.32	0.292	0.771
Course of disease, months	10.27 ± 2.61	10.77 ± 1.89	0.981	0.329
Visual acuity	0.528 ± 0.43	0.536 ± 0.48	0.079	0.937
Gender (Male/Female)	22/18	23/17	0.051	0.822
Mean HbA1c, %	8.90 ± 1.26	8.50 ± 1.22	1.442	0.153

blood glucose < 9 mmol/L and postprandial blood glucose < 12 mmol/L).

Exclusion criteria

(1) Non-DR patients; (2) Patients with glaucoma, retinal detachment, optic nerve disease, or other eye disease; (3) Patients with uncontrolled hyperglycemia; (4) Patients with severe heart, liver, kidney, or hematopoietic system diseases; (5) Patients who had undergone surgical treatment; (6) Patients who were allergic to the study drug or had a history of drug allergy; or (7) Pregnant or lactating women.

According to the inclusion and exclusion criteria, a total of 80 patients involving 111 eyes were enrolled. Based on the treatment approach, these patients were divided into a control group (40 cases, 56 eyes, routine control of blood glucose) and an experimental group (40 cases, 55 eyes, routine control of blood glucose + PGMS). PGMS was administered orally at a dose of 100 mg, three times a day for 60 days, as one course of treatment. The control group comprised 23 men and 17 women, averaging 61.27 ± 8.53 years in age, with a disease duration of 10.27 ± 2.61 months and an initial visual acuity of 0.528 ± 0.43. The experimental group included 22 men and 18 women, with an average age of 62.25 ± 8.32 years, a disease duration of 10.77 ± 1.89 months, and an initial visual acuity of 0.536 ± 0.48. There was no significant difference in gender, age, or disease duration between the two groups (**Table 1**).

Data collection

All patients underwent ophthalmic examinations upon admission, including best-corrected visual acuity, fundus examination and photography, and fundus angiography. These examinations were repeated after a 60-day course of oral PGMS administration.

Observation indices and criteria

Primary outcomes: The clinical efficacy was compared between the two groups after treatment. The visual acuity was examined by the same doctor using methods outlined in the *Progress in the Treatment of Diabetic Retinopathy* [12], and the fundus angiography and visual acuity chart data were used as the evaluation basis. Treatment was considered significantly effective (SE) if the symptoms such as fundus microhemangioma, hemorrhage, and hard exudates largely resolved, as well as the visual acuity being improved by at least three lines. Treatment was considered commonly effective (CE) if microhemangioma, hemorrhage, hard exudates and other symptoms partially resolved and visual acuity was improved by one or two lines. Treatment was considered ineffective if symptoms remained unchanged or worsened, and visual improvement did not meet the above criteria.

The total effective rate (TER) = (SE cases + CE cases)/Total cases × 100%.

Secondary outcomes: The blood glucose, glycosylated hemoglobin, visual acuity, hemorrhage area, and the area of non-perfusion were compared between the two groups before and 1 week after treatment. Color fundus photography was conducted to observe the hemorrhage area according to the standard seven-zone method of the University of Wisconsin Fundus Imaging Center [13]. The photography protocol stipulated a shooting angle between 30° and 55° and pupil dilation to at least 5.5 mm. After the fundus image was obtained, the fundus image analysis software was used to create a mosaic according to the standard seven areas, manually correcting and eliminating the repeated areas. The software automatically captured the hemorrhage area, and the pixels of the hemorrhage area were obtained after manual correction. The same method was used to analyze the fundus angiography images to obtain an image of the non-perfusion area.

Statistical analysis

Stata 12.0 statistical software (StataCorp LLC, College Station, TX, USA) was used for data

Table 2. Comparison of the blood glucose between the two groups

	Fasting blood-glucose (mmol/L)		Glycosylated hemoglobin (%)	
	Before treatment	After treatment	Before treatment	After treatment
Experience group	8.43 ± 0.35	6.71 ± 0.47	8.90 ± 1.26	6.40 ± 0.62
Control group	8.36 ± 0.40	7.50 ± 0.51	8.50 ± 1.22	5.95 ± 0.44
t	0.833	7.204	1.442	3.743
P	0.407	< 0.0001	0.153	0.0003

Table 3. Comparison of eyesight improvement between the two groups after PGMS treatment

Group name	Quantity	Improved by ≥ 3 lines	Improved by ≥ 1 lines	Unchanged	Deteriorated
Experimental group	56	8	29	14	5
Control group	55	3	14	23	15
χ^2			14.693		
P			0.002		

Table 4. Comparison of macular retinal thickness between the two groups after treatment

Group name	Quantity	Thickness reduction > 100 μm	100 μm > Thickness reduction > 50 μm	Thickness reduction < 50 μm	Thickness increase
Experimental group	56	5	23	16	12
Control group	55	2	12	24	17
χ^2			7.108		
P			0.008		

analysis. Measurement data were presented as mean ± standard deviation, paired sample t test was used for intra-group comparison, while independent sample t test was used for inter-group comparison. Enumeration data were expressed as percentages (%), and the chi-squared test was used. $P < 0.05$ indicated statistical significance.

Results

Comparison of blood glucose levels between the two groups before and after treatment

Before treatment, there was no significant differences in blood glucose levels and glycosylated hemoglobin levels between the two groups (P=0.407, P=0.153); after treatment, the fasting blood glucose and glycosylated hemoglobin levels of the experimental group were significantly lower than those of the control group (both $P < 0.001$) (**Table 2**).

Comparison of visual acuity between the two groups before and after treatment

Before the treatment, there was no significant difference in visual acuity between the two groups (P=0.937, **Table 1**). However, after PGMS treatment, substantially more patients in the experimental group showed significant improvements in eyesight than that of the control group (P=0.002) (**Table 3**).

Comparison of the macular retinal thickness between the two groups before and after treatment

After treatment, substantially more patients experienced notable reduction (> 50 μm) in macular retinal thickness in the experimental group compared with the control group (P=0.008) (**Table 4**). The change in macular thickness before and after treatment is shown in **Figure 2**, revealing a reduction in the thickness of macular area, with clear boundary.

Comparison of clinical efficacy between the two groups

The total clinical efficacy rate of the experimental group was 67.86%, which was significantly higher than 38.18% of the control group (P=0.032) (**Table 5**). The comparison of fundus images before and after treatment is shown in **Figure 3**, revealing a reduction in macular hemorrhage and hard infiltration.

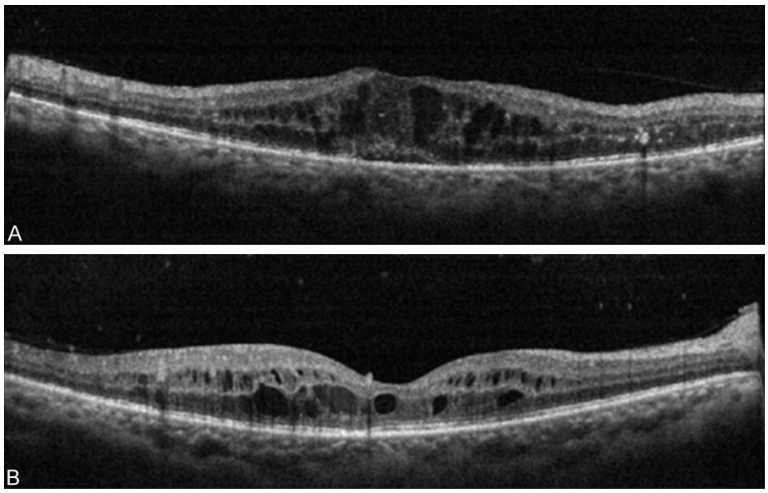

Figure 2. Comparison of macular thickness before and after PGMS treatment of a 56-year-old male patient. A: Before PGMS treatment; B: After PGMS treatment.

Table 5. Comparison of clinical efficacy of both groups

Group name	Quantity	Significantly effective	Effective	Invalid
Experimental group	56	6	32	18
Control group	55	2	19	24
χ^2		4.612		
P		0.032		

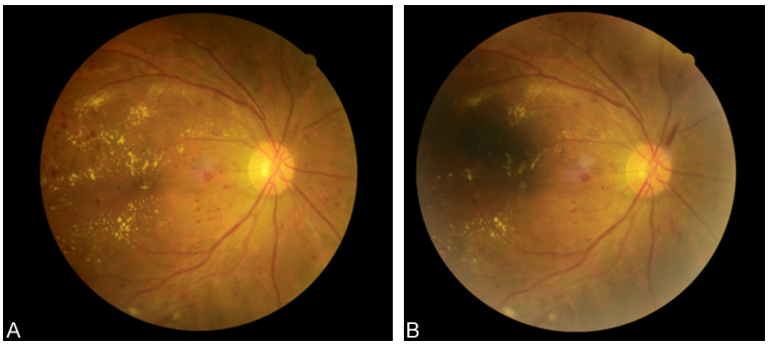

Figure 3. Comparison of eye fundus images before and after treatment of a 65-year-old female patient. A: Before PGMS treatment; B: After PGMS treatment; Macular hemorrhage and hard infiltration were significantly reduced after treatment.

Discussion

Diabetic retinopathy (DR) is the most prevalent microvascular complication of diabetes and has garnered considerable attention due to its detrimental effects [14]. However, current treatments of DR are mostly unsatisfactory, mainly involving early-stage retinal photocoagulation and late-stage vitrectomy. Effective pharmacological interventions remain under investigation. Recent research has increasingly recognized DR as an inflammation-related disease. Hyperglycemia promotes leukocyte aggregation in retinal tissue, leading to the production of inflammatory factors and triggering a subsequent inflammatory response, in which inflammatory factors play an important role. The excessive expression of inflammatory factors can damage the diabetic retina [15]. Chronic hyperglycemia causes metabolic abnormalities in the DR, including activation of the polyol pathway, hexosamine biosynthesis pathway, and protein kinase C pathway, as well as the accumulation of advanced glycosylation end products (AGEs). These processes result in an increase in reactive oxygen species in the cells, and an increase in retinal oxidative stress and inflammation [16-18]. It was reported in the literature that the inflammatory factors, interleukin-1β and tumor necrosis factor α, are closely related to the occurrence and development of DR [19, 20]. Even mild inflammation can trigger a series of cellular abnormalities and tissue damage, culminating in retinal deterioration [21-24].

In DR, vascular endothelial growth factor (VEGF), a secreted factor that increases the mitogenic activity of vascular endothelial cells, is a potent pro-angiogenic factor. It is involved in the development of DR by altering the structure and function of the vascular endothelium, increasing the permeability of capillaries, and promoting the synthesis of extracellular matrix, as well as inducing retinal neovascularization and increasing the permeability of retinal blood vessels [25-27]. In the healthy state, VEGF is weakly expressed in the eye, where it plays a role in maintaining the integrity of the ocular vascula-

ture. However, it is overexpressed in the pathological state, leading to abnormal neovascularization in the eye, making it a pivotal element in the pathogenesis of DR, especially in its early stages. This includes its influence on free radical metabolism, lipids, and inflammatory factor levels in diabetes mellitus [28].

Propylene glycol mannate sulfate (PGMS) is a new type of low molecular weight acidic polysaccharide drug developed by the Ocean University of China on the basis of dibasic sodium alginate (PSS), exhibiting anticancer, antibacterial, anti-inflammatory, immune and antiaging effects [29]. Studies have shown that PGMS can inhibit the excessive proliferation of vascular smooth muscle cells, protect vascular endothelial cells, and reduce patients' erythrocyte filtration index and erythrocyte membrane lipid peroxide levels. Moreover, it can increase the activity of GSH Px and Na^+-K^+-ATPase, reduce lipid peroxide (MDA) levels, increase the activity of SOD and GSH Px, reduce brain water content, improve immune function, reduce blood lipids, and resist thrombosis [30]. PGMS can be rapidly absorbed by oral administration, exhibiting a high plasma protein binding rate and bioavailability.

Experiments have shown that PGMS effectively shields vascular endothelial cells from inflammatory factors and various chemicals [31]. Studies have shown that glycol can inhibit the expression of inflammatory factors in the kidneys of diabetic rats [32], while additional clinical research has indicated that glycosyl esters can reduce the level of blood lipids and inflammatory factors in peripheral blood in diabetic patients [7]. Also, in this study, after treatment, fasting blood glucose and glycosylated hemoglobin levels were lower in the experimental group than in the control group. These results suggest that in patients with non-proliferative DR, PGMS not only helps manage blood glucose levels but also appears to control microvascular complications. It is thought to fortify and activate blood circulation, remove blood stasis, regulate glucose metabolism, and thus stabilize blood glucose levels, positively impacting fasting blood glucose and glycosylated hemoglobin levels.

There are certain limitations to this study: (1) The retrospective nature of the analysis precluded the randomization of patient groups, affecting the homogeneity within each group. (2) Being a single center analysis with a small sample size, this study only observed short-term effects without addressing long-term efficacy. Future studies should expand the sample size, extend follow-up time, and evaluate long-term treatment. (3) There are few observation indicators in this study. In future research, serum cytokines, VEGF protein expression and other indicators can be added to evaluate the therapeutic efficacy of PGMS from multiple aspects.

Conclusion

PGMS has a significant effect on improving the vision of patients with non-proliferative diabetes retinopathy, promoting the absorption of fundus hemorrhage and exudation, and restoring oxygen supply to the retina. Therefore, PGMS appears to hold therapeutic potential for non-proliferative DR.

Disclosure of conflict of interest

None.

Address correspondence to: Haining Xu, Department of Ophthalmology, Weihaiwei People's Hospital, Weihai, Shandong, China. E-mail: 18563-110528@163.com

References

[1] Basu S, Zethelius B, Helmersson J, Berne C, Larsson A and Arnlöv J. Cytokine-mediated inflammation is independently associated with insulin sensitivity measured by the euglycemic insulin clamp in a community-based cohort of elderly men. Int J Clin Exp Med 2011; 4: 164-168.

[2] Shaw JE, Sicree RA and Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010; 87: 4-14.

[3] Yang W, Lu J, Weng J, Jia W, Ji L, Xiao J, Shan Z, Liu J, Tian H, Ji Q, Zhu D, Ge J, Lin L, Chen L, Guo X, Zhao Z, Li Q, Zhou Z, Shan G and He J; China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. N Engl J Med 2010; 362: 1090-1101.

[4] Sahakyan K, Klein BE, Lee KE, Tsai MY and Klein R. Inflammatory and endothelial dysfunction markers and proteinuria in persons with type 1 diabetes mellitus. Eur J Endocrinol 2010; 162: 1101-1105.

[5] Tapp RJ, Shaw JE, Harper CA, de Courten MP, Balkau B, McCarty DJ, Taylor HR, Welborn TA and Zimmet PZ; AusDiab Study Group. The prevalence of and factors associated with diabetic retinopathy in the Australian population. Diabetes Care 2003; 26: 1731-1737.
[6] Huang J and Xie LN. Inhibitory effect of propylene glycol mannate sulfate on growth of rabbit lens epithelial cells in vitro. Int J Ophthalmol 2010; 3: 54-57.
[7] Gao Y, Zhang L and Jiao W. Marine glycan-derived therapeutics in China. Prog Mol Biol Transl Sci 2019; 163: 113-134.
[8] Wang RX, Hu JT, Gao L, Zhao JJ and Zhang XM. Propylene glycol mannate sulfate down-regulated the expression of adhesion molecules (ICAM-1, VCAM-1) in kidney of diabetic rats. Chin J Marine Drug 2005; 24: 10-16.
[9] Chen XM, Pan JQ and Zhang ZN. Effects of propylene glycol mannate sulfate on thrombosis in abdominal aorta in rabbits. Zhongguo Yao Li Xue Bao 1995; 16: 226-230.
[10] Gao Y, Yu WG, Han F, Lu XZ, Gong QH and Guan HS. Inhibition of MCP-1 mRNA expression by propylene glycol mannate sulfate in hyperlipidemic rat aorta. Yao Xue Xue Bao 2003; 38: 582-585.
[11] 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 number 10. Ophthalmology 2020; 127: S99-S119.
[12] Al-Shabrawey M, Zhang W and McDonald D. Diabetic retinopathy: mechanism, diagnosis, prevention, and treatment. Biomed Res Int 2015; 2015: 854593.
[13] Himasa FI, Singhal M, Ojha A and Kumar B. Prospective for diagnosis and treatment of diabetic retinopathy. Curr Pharm Des 2022; 28: 560-569.
[14] Gardner TW, Sander B, Larsen ML, Kunselman A, Tenhave T, Lund-Andersen H, Reimers J, Hubbard L, Blankenship GW, Quillen DA, Brod RD, Wilmarth MH, Post-Hansen H, Parving HH and Davis MD. An extension of the early treatment diabetic retinopathy study (ETDRS) system for grading of diabetic macular edema in the astemizole retinopathy trial. Curr Eye Res 2006; 31: 535-547.
[15] Klein BE. Overview of epidemiologic studies of diabetic retinopathy. Ophthalmic Epidemiol 2007; 14: 179-183.
[16] Garg SS and Gupta J. Polyol pathway and redox balance in diabetes. Pharmacol Res 2022; 182: 106326.
[17] Wang Y, Eshwaran R, Beck SC, Hammes HP, Wieland T and Feng Y. Contribution of the hexosamine biosynthetic pathway in the hyperglycemia-dependent and -independent breakdown of the retinal neurovascular unit. Mol Metab 2023; 73: 101736.
[18] Kang Q and Yang C. Oxidative stress and diabetic retinopathy: molecular mechanisms, pathogenetic role and therapeutic implications. Redox Biol 2020; 37: 101799.
[19] Adachi T, Yasuda H, Nakamura S, Kamiya T, Hara H, Hara H and Ikeda T. Endoplasmic reticulum stress induces retinal endothelial permeability of extracellular-superoxide dismutase. Free Radic Res 2011; 45: 1083-1092.
[20] Myśliwiec M, Zorena K, Balcerska A, Myśliwska J, Lipowski P and Raczyńska K. The activity of N-acetyl-beta-D-glucosaminidase and tumor necrosis factor-alpha at early stage of diabetic retinopathy development in type 1 diabetes mellitus children. Clin Biochem 2006; 39: 851-856.
[21] Altmann C and Schmidt MHH. The role of microglia in diabetic retinopathy: inflammation, microvasculature defects and neurodegeneration. Int J Mol Sci 2018; 19: 110.
[22] Forrester JV, Kuffova L and Delibegovic M. The role of inflammation in diabetic retinopathy. Front Immunol 2020; 11: 583687.
[23] Wang W and Lo ACY. Diabetic retinopathy: pathophysiology and treatments. Int J Mol Sci 2018; 19: 1816.
[24] Whitehead M, Wickremasinghe S, Osborne A, Van Wijngaarden P and Martin KR. Diabetic retinopathy: a complex pathophysiology requiring novel therapeutic strategies. Expert Opin Biol Ther 2018; 18: 1257-1270.
[25] Martinez-Zapata MJ, Salvador I, Martí-Carvajal AJ, Pijoan JI, Cordero JA, Ponomarev D, Kernohan A, Solà I and Virgili G. Anti-vascular endothelial growth factor for proliferative diabetic retinopathy. Cochrane Database Syst Rev 2023; 3: CD008721.
[26] Chatziralli I and Loewenstein A. Intravitreal anti-vascular endothelial growth factor agents for the treatment of diabetic retinopathy: a review of the literature. Pharmaceutics 2021; 13: 1137.
[27] Abu-Yaghi NE, Abu Tarboush NM, Abojaradeh AM, Al-Akily AS, Abdo EM and Emoush LO. Relationship between serum vascular endothelial growth factor levels and stages of diabetic retinopathy and other biomarkers. J Ophthalmol 2020; 2020: 8480193.
[28] Andrés-Blasco I, Gallego-Martínez A, Machado X, Cruz-Espinosa J, Di Lauro S, Casaroli-Marano R, Alegre-Ituarte V, Arévalo JF and Pinazo-Durán MD. Oxidative stress, inflammatory, angiogenic, and apoptotic molecules in proliferative diabetic retinopathy and diabetic macular edema patients. Int J Mol Sci 2023; 24: 8227.

[29] Gao Y, Yu WG, Han F, Lu XZ, Gong QH, Hu XK and Guan HS. Effect of propylene glycol mannate sulfate on blood lipids and lipoprotein lipase in hyperlipidemic rat. Yao Xue Xue Bao 2002; 37: 687-690.
[30] Patel JI, Saleh GM, Hykin PG, Gregor ZJ and Cree IA. Concentration of haemodynamic and inflammatory related cytokines in diabetic retinopathy. Eye (Lond) 2008; 22: 223-228.
[31] Zhe W, Kui-Chen C and Ling G. Effects of propylene glycol mannate sulfate on adhesion molecules--CD_(54), CD_(106), CD_(62p) in diabetic rats. Chin J Marine Drug 2003.
[32] Fusman R, Rotstein R, Zeltser D, Prochorov V, Shapira I, Bornstein NM, Keren G, Roth A, Miller HI, Avitzour D, Arber N and Berliner S. The state of leukocyte adhesiveness/aggregation in the peripheral blood of patients with type 2 diabetes and ischemic vascular disease. Acta Diabetol 2001; 38: 43-49.