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Review Article

Clinical Expression Analysis of Serum miR-29b and miR-126 in Patients with Non-Proliferative Diabetic Retinopathy

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ABSTRACT

Circulating miRNA remains stable and can affect glucose and lipid metabolism, inflammatory response, and angiogenesis pathways in diabetic patients by participating in energy metabolism, insulin synthesis, transportation, and signal transduction. It plays a crucial role in the occurrence and development of diabetes and its complications. This study aims to systematically evaluate the efficacy and safety of integrated traditional Chinese and Western medicine in treating non-proliferative diabetic retinopathy (NPDR). Our study used a descriptive-analytical technique and established a corresponding model diagram to analyze and study diabetic retinopathy. We examined non-value-added DR based on integrated traditional Chinese and western medicine. Further analysis and research on the retina of non-value-added diabetes mellitus. Lastly, we analyzed miR-29b and miR-126 in DR. Red blood cell aggregation can lead to arteriolar embolism and uncompensated collateral circulation of retinal capillaries due to the inability to pass through capillaries with a diameter of 3.5-6.0μm. Large infarct areas can cause capillary occlusion, which manifests as a patchy and flaky fluorescent dark area on fluorescein angiography, indicating capillary perfusion-free areas. The related risk factors of DR are closely related to the patient's overall condition, such as the course of the disease, age, blood sugar, glycosylated hemoglobin, blood lipid, and renal function. The results of this study show that MiR-29 and DR have a significant correlation, with an influence as high as 54.42%. The dysregulation of MiR-29b and Rax and the activation of the NF-κB signaling pathway may contribute to the development and progression of DR. Our study provides a foundation for future research and treatment of patients with NPDR.

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YL conceived, designed the analysis and wrote the paper. XZ contributed data, performed the analysis and proofread the paper.

Key words
NPDR, DR, MiR-29, MiR-26, Serum, Traditional Chinese, Western medicine

INTRODUCTION

Diabetic retinopathy (DR) is one of the common microvascular complications of diabetes, and it is a disease with a high disability rate among diabetic patients (Naghizadeh *et al*., 2018; Sheng *et al*., 2020). Its pathogenesis is still unclear. Currently, there are as many as 100 million diabetic patients worldwide, and this number is increasing by millions every year (Hajilou *et al*., 2021). DR is a serious microvascular complication of diabetes, and it is also a significant cause of blindness in people over 50 (Alzahrani *et al*., 2018; Kropp *et al*., 2023). Its incidence rate is rapidly increasing due to the rising prevalence of diabetes and longer lifespan. The disease can cause severe visual impairment, significantly affecting patients' quality of life and ability to work (Ghanbari *et al*., 2023).

To prevent the occurrence and slow down the progression of DR, it is essential to explore the relationship between DR and fasting blood glucose (FBG), postprandial blood glucose (2h PBG), and glycosylated hemoglobin (HbA1c) and to identify effective blood glucose control targets for patients with DR (Haddadinezhad and Ghazaleh, 2010; Ketema and Kebrat, 2015).

Retinal laser photocoagulation is an internationally recognized and important local treatment method for DR, but its therapeutic effects vary greatly, and the reasons for this variation are complicated (Lin *et al*., 2023; Huang *et al*., 2020). The side effects and complications of DR

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treatments can seriously threaten the visual prognosis of patients. Type 2 diabetes is a metabolic disease characterized by elevated blood sugar, which can lead to various complications with disease progression. DR is a common and severe complication of diabetes, and it is a significant cause of vision loss and blindness, which can seriously affect patients' quality of life. Therefore, early prevention and control of DR is crucial (Harrison *et al*., 2011; Wiley and Ferris, 2013).

Current research shows that DR is a complex pathological process that involves inflammatory reactions, neovascularization, and cell fibrosis (Van Hove *et al*., 2021; Gucciardo *et al*., 2018). MicroRNA, a non-coding RNA molecule, is widely involved in biological processes such as cell proliferation, migration, and apoptosis (Khoo *et al*., 2019).

DR is the main cause of blindness, and its prevalence is high in China. The specific pathogenesis of DR is not entirely clear, which seriously impacts patients' physical and mental health and quality of life (Singla, 2022; Park *et al*., 2017). It is essential to identify relevant markers of blindness for diagnosing and treating DR. MicroRNA, as a highly conserved short RNA, plays a crucial role in many biological behaviors such as cell proliferation, apoptosis, tumorigenesis, immune response, and angiogenesis (Park *et al*., 2017). Early prevention, control, and identifying relevant markers of DR blindness are crucial in managing diabetes-related complications.

MicroRNA is an endogenous, non-coding, single-stranded small-molecule RNA that participates in almost all physiological and pathological processes in organisms, including cell growth, development, proliferation, differentiation, and apoptosis (Dong and Cong, 2021; Wang *et al*., 2018; Beylerli *et al*., 2022). It mainly functions by inhibiting the translation or degradation of target mRNA. DR is one of the main chronic microvascular complications of diabetes and the leading cause of blindness in adults (Wang *et al*., 2018). In recent years, the incidence of diabetes in China has gradually increased, increasing the prevalence and blindness rate of DR (Lin *et al*., 2019). Current western medicine treatments for DR involve drugs, laser therapy, vitrectomy, anti-vascular endothelial growth factor therapy, and intraocular steroid injection combined with strict control of blood sugar, blood pressure, and blood lipid levels. However, this treatment is expensive and not entirely effective (Park *et al*., 2017).

TCM can treat early DR based on syndrome differentiation, which has unique advantages in improving vision, delaying the progression of DR, promoting the improvement of pathological fundus changes, improving systemic symptoms, and enhancing the quality of life (Man and Sai, 2022; Liu *et al*., 2020; Li *et al*., 2022). Combining traditional chinese and western medicine can complement each other's strengths and weaknesses in treating early DR, leading to good clinical outcomes (Tejerina *et al*., 2015).

Our study employs various research methods to study and analyze DR. The research involves establishing corresponding algorithmic formulas and model diagrams to aid in further research and explanation. Additionally, data analysis is carried out, and corresponding data tables and graphs are established for further analysis. The main objective was to analyze DR based on clinical evidence and academic publications, and to analyze the characteristics of MicroRNAs implicated in DR.

RELATED WORK

Diabetes mellitus has gradually become a chronic epidemic without detection. According to preliminary statistics, the total number of diabetic patients worldwide had reached 415 million by 2015, with China alone accounting for about 1/7, ranking first globally. It is predicted that the number of diabetic patients worldwide will surge to 552 million by 2030. DR is a characteristic change of micro vessels in patients with DM (Klein *et al*., 2008). Its main pathological changes include pericyte apoptosis and basement membrane thickening, which weakens the vascular wall's function.

DR is mainly caused by non-functional or proliferating unhealthy blood vessels, leading to the leakage of liquid and lipids in the blood and cells into the retina. When the leakage involves the posterior polar retina or macula, it can cause visual function damage (Zheng *et al*., 2021). Mammalian genomes can encode about 1,100 kinds of miRNAs, regulating about 60% of proteins encoded by genes. miRNA can be expressed in all human cells, mainly regulating gene expression by promoting messenger RNA degradation and inhibiting its expression (Davis-Dusenbery and Hata, 2010; O'Brien *et al*., 2018). Vascular endothelial growth factor (VEGF) is a dimeric glycoprotein that widely exists in various human tissues (Kaufman *et al*., 2021). It plays an essential role in forming new blood vessels and can be produced in large quantities under tissue hypoxia (Zhao *et al*., 2022). VEGF is recognized as one of the most essential angiogenesis factors, and it is crucial for forming new blood vessels in various eye tissues.

Galicia-Garcia *et al*. (2020) proposed that hyperlipidemia can alter the lipid structure of the cell membrane, leading to endothelial dysfunction and tissue peroxidation via the non-enzymatic glycosylated polyol pathway. This can damage the blood vessel wall, micro thrombosis, and destruction of the retinal barrier. The destruction of the retinal barrier can also cause plasma

lipoproteins and crystalline substances (Lyons and Jenkins, 1997).

Although there is much TCM syndrome differentiation and typing methods for DR, there is no unified standard, and different prescriptions are chosen according to the different views of doctors. However, the advantages and characteristics of TCM in treating DR are irreplaceable. TCM has a remarkable effect in improving retinopathy and clinical symptoms and plays a multi-target and overall regulatory role in the prevention and treatment of DR (Ma *et al*., 2022).

Huang *et al*. (2023) proposed that FFA examination is necessary for the staging of DR. FFA has significant advantages over ophthalmoscopy in detecting capillary micro angiomas, non-perfusion areas of capillaries, and retinal neovascularization and can be used for the early diagnosis of DR. Zhao *et al*. (2020) suggest that miR-29b may play a role in the process of DR angiogenesis by upregulating FGF expression.

As the course of the disease prolongs, the probability of DR in type 2 diabetes mellitus (T2DM) patients increases. Poor control of blood sugar levels is an essential reason for the occurrence of DR (Bain *et al*., 2019). Fasting plasma glucose (FPG) is not an independent risk factor for the occurrence of DR, and it is related to patients differences (Yu *et al*., 2023).

Giri *et al*. (2018) proposed that the onset of DR results from multiple factors, including hyperglycemia, metabolic abnormalities, non-enzymatic glycosylation of protein, hemodynamic disorder, oxygen-free radical formation, abnormal coagulation mechanism, and angiogenesis factors. Previous studies have shown that early microglia activation in the retina and the expression of interleukin-18 mRNA and its protein increase, indicating that retinopathy may be caused by genes that regulate the migration and localization of neovascular endothelial cells (Wooff *et al*., 2019; Bereimipour *et al*., 2021).

ANALYSIS OF NON-PROLIFERATIVE DIABETIC RETINOPATHY (NPDR)

Non-value-added DR based on integrated traditional Chinese and western medicine

In the past few decades, the prevalence of DR in developing countries has been increasing yearly, seriously endangering people's quality of life. Therefore, active treatment in the NPDR stage is critical to delay the development of this disease (Torus *et al*., 2020). Western medicine mainly treats this disease by lowering blood sugar and improving the microcirculation of the eyes to inhibit the formation of new blood vessels. However, the side effects are significant, and it is easy to relapse.

According to the difference in the individual constitution, TCM treatment based on syndrome differentiation has a good effect on this disease. People have widely recognized combining traditional chinese and western medicine as safe and effective clinical means in recent years. Western medicine mainly adopts systemic treatment for NPDR and strictly controls blood sugar with drugs and diet. Local therapies such as laser therapy and vitrectomy should be considered for PDR. However, the overall curative effect of these methods is not ideal.

The related risk factors of DR are closely related to the patient's overall condition, such as the course of the disease, age, blood sugar, glycosylated hemoglobin, blood lipid, and renal function (Klein *et al*., 2008). For example, the level of glycated hemoglobin, macrophage migration inhibitory factor, and urinary microalbumin in diabetic patients is positively correlated with the condition of DR, which can be used to improve clinical symptoms and reproductive quality (Lu *et al*., 2019).

Many patients have to take or inject various drugs besides photocoagulation, and their clinical symptoms still cannot be relieved. After adding TCM, patients' symptoms improved, helping them to build up their confidence in overcoming diseases and forming an optimistic mood. In this research, a corresponding model diagram is established to analyze and study DR, such as in the cases of Kim Hye Yoon and Escape Room: Tournament of Champions.

The threat of DR to vision is well known, and patients who progress to the proliferative stage suffer great pain in reproduction and treatment. Laser photocoagulation is internationally recognized as the most effective and essential local treatment method for DR (Lin *et al*., 2023; Huang *et al*., 2020). It has formed a set of relatively mature treatment principles and norms. The mechanism is that the photocoagulation in the thermal effect of laser biology destroys part of the outer retina with vigorous metabolism (Lin *et al*., 2023). The rod and cone cells with high oxygen consumption are replaced by scar tissue, which reduces the oxygen consumption of the retina (Huang *et al*., 2020). After photocoagulation, the retina becomes thinner, helps oxygen and nutrients diffuse from choroidal circulation to the inner retina, improves retinal circulation, and reduces the production of new blood vessel growth factors that stimulate the formation of new blood vessels. It prevents the formation of new blood vessels and the further development of DR.

The incidence of diabetes and related deaths will become society's main health problem. Diabetes can lead to systemic complications involving multiple systems (McNamara *et al*., 2019). Continuous high-sugar environments can lead to macrovascular and microvascular complications. Patients with diabetes accelerate the

process of atherosclerosis and hypertension, leading to macrovascular complications such as cardiovascular degeneration, coronary atherosclerosis, and stroke. Microvascular complications include DR, which leads to vision loss or loss, and diabetic nephropathy, which damages nephrons and eventually leads to renal failure. Microvascular-related complications are also manifested in pathological and physiological changes, such as diabetic neuropathy caused by the involvement of the nervous system, such as a diabetic foot.

Calcium dobesilate significantly improves retinal hemorrhage and vision. However, it cannot improve and reduce micro angioma, fundus capillary occlusion, visual field, and intraocular pressure (Wang *et al*., 2022). As calcium dobesilate is mainly a vascular protective agent, it can stabilize retinal circulation and improve retinal hemorrhage and exudation (Stitt *et al*., 2016). The formation of micro aneurysms is primarily due to the abnormal proliferation of local endothelial cells (Mrugacz *et al*., 2021; Santiago *et al*., 2018). The causes of capillary occlusion may be that many harmful factors cause metabolic changes in capillary cells, pericytes die, endothelial cells are damaged, and capillaries with no cell structure appear (Santiago *et al*., 2018).

Studies on the retina of non-value-added diabetes mellitus

Clinical trials have identified calcium dobesilate as a potential vascular protector that can improve retinal blood circulation, stabilize the retinal barrier, reduce the high permeability of retinal blood vessels and capillary fragility, and prevent exudation and internal/external arterial bleeding (Leal *et al*., 2010). However, the methodological quality of all included trials is inadequate, as they only partially meet quality standards and have a moderate bias. Common problems include the lack of specific descriptions of randomization methods, concealment of the random allocation scheme, and sketchy details on lost visits.

Diabetes mellitus (DM) is a systemic disease affecting many systemic organs during its occurrence and development, with interrelated complications (Zhang *et al*., 2021). Long-term exposure to high glucose can lead to several vascular diseases, among which vascular endothelial cell injury is prevalent and is a common trigger of atherosclerosis (Zhao *et al*., 2022). Basement membrane thickening, microcirculation disturbance, and nutrient nerve blood vessel injury contribute to ischemic and hypoxic nerve fibers, which can cause diabetic neuropathy (Zhang *et al*., 2021). In addition, the injury of the basement membrane and endothelial cells can cause pathological changes in the body's micro-vessels, promoting the occurrence of DR and diabetic nephropathy. Therefore, the study compared the total effective rate of the combination treatment group of chinese and western medicine and the treatment group of western medicine alone, and the differences were shown in the formulae below;

$$\mathrm{OR} = \mathrm{CI}(1.91, 1.49), \mathrm{P} = 0, 02. \mathrm{Z} = 2.87 \quad \ldots(1)$$

$$\mathrm{P} = 0.002 + \mathrm{Z} = \mathrm{I}^2 \quad \ldots(2)$$

Through the patient's research and analysis, the random effect model is adopted, as shown in the formulas;

$$\mathrm{SMD} = 0.44, 94\%\ \mathrm{CI}\ (0.31\ \mathrm{M}\ 0.74), \mathrm{P} = 0.001, \mathrm{Z} = 4.3 \quad \ldots(3)$$

$$\mathrm{P} = 0.001 * \mathrm{CI} + \mathrm{Z} = \mathrm{I}^2 \quad \ldots(4)$$

The study shows that the changes in whole blood viscosity before and after treatment are heterogeneous among the studies. The random effect model is shown in the formulas below:

$$\mathrm{SMD} = -0, 47, 94\ \%\ \mathrm{CI}\ (-0.58, -0.25), \mathrm{P} = 0.001, \mathrm{Z} = 4.47 \quad \ldots(5)$$

$$P = 0.001 - Z = I^2 = 0 \quad \ldots(6)$$

Through research, we can know the change in whole blood viscosity before and after treatment. Compared with western medicine, the combination of traditional chinese and western medicine can reduce the whole blood viscosity of patients, and it is also shown in formulas;

$$\mathrm{SMD} = -0.45, 94\%\mathrm{CI}\ (-0.75, -0.12), \mathrm{P} = 0.004, \mathrm{Z} = 2.55 \quad \ldots(7)$$

$$\mathrm{P} = 0.000, \mathrm{Z}, = \mathrm{I}^2 \quad \ldots(8)$$

$$\mathrm{SMD} = -1.35, 94\%\ \mathrm{CI}\ (-2.30, -0.40) \quad \ldots(9)$$

$$\mathrm{SMD} = \mathrm{CI}, \mathrm{P} = 0.000, \mathrm{Z} = 2.87 \quad \ldots(10)$$

NPDR is characterized by damage to the fundus micro-vascular structure, which leads to vasodilatation, leakage, or rupture (Pearce, 2021; Nawaz *et al*., 2019). Western medicine mainly treats this disease with calcium dobesilate, protein kinase C blocker, glucocorticoid, and VEGF inhibitor. Glucocorticoids can inhibit the over-expression of VEGF, compact capillary endothelial cells, and regulate the blood-retinal barrier (Marchesi *et al*., 2018). However, long-term use will cause adverse reactions such as increased intraocular pressure and white lens formation; Protein kinase C blockers can block VEGF receptors, but it will cause nausea and diarrhea. Traditional Chinese medicine has rich experience and unique advantages in treating this disease (Tables I, II).

The unique advantages of TCM in treating DR are mainly reflected in the dialectical treatment approach and the prolonged action of drug potency (Man and Sai, 2022). By treating the symptoms, the drug potency acts on the body over a longer period, alleviating the toxic and side effects caused by long-term Western medicine use.

Laser photocoagulation is internationally recognized as the most effective and essential local treatment method for DR, and a set of relatively mature treatment principles

and norms have been established (Lin *et al*., 2023; Huang *et al*., 2020). The mechanism involves the thermal effect of laser biology destroying the part of the outer retina with vigorous metabolism, which replaces the rod cells and cone cells with high oxygen consumption with scar tissue, thereby reducing the oxygen consumption of the retina (Huang *et al*., 2020). Additionally, photocoagulation helps oxygen and nutrients diffuse from choroidal circulation to the inner retina, improves retinal circulation, reduces the production of new blood vessel growth factors that stimulate the formation of new blood vessels, and prevents the further development of DR (Huang *et al*., 2020).

Table I. Comparison of clinical features and biochemical blood indices.

Variable	NPDR	NDR	T value
BMI	8.43	22.45	2.12
TC	23.4	5.45	0.72
TG	7.67	2.51	1.50
Lp	407.23	302.2	22.98

Table II. Comparison of clinical features and biochemical blood indices.

Variable	NPDR	NDR	P值
HDL-C	1.87	1.87	0.37
LDL-C	2.68	2.65	0.78
Systolic pressure	141.3	128.2	0.118

Studies have found that quercetin can inhibit the phosphorylation of protein kinase C, ERK1, and cytosol C *in vivo*, protect the blood-retinal barrier, and improve fundus microcirculation through the ACP/MTOR/Ma Yili 70S6K signal pathway of VEGFR-2 (Cheng *et al*., 2019). Sitosterol can regulate lipid metabolism, protect vascular endothelial cells, and reduce cholesterol and triglyceride levels. Xuefuzhuyu decoction can inhibit the levels of inflammatory factors MIF and TNF-α in Kramp-Karrenbauer and Benchang You, reduce the damage of inflammatory, stimulating factors to optic nerve cells, and protect cell inner and basement membranes.

Xuefu Zhuyu Decoction can also improve the glucose and lipid metabolism of NPDR patients, reduce inflammatory reactions, and improve eyesight (Ye *et al*., 2020). Similarly, clinical methods such as activating blood circulation to remove blood stasis, invigorating qi, nourishing yin, soothing the liver and regulating qi, and nourishing the liver and kidney have achieved sound clinical effects. Kim Hye Yoon, 14, Kramp-Karrenbauer, 15, and Cho Jung Seok are involved in the research and analysis of Mir.

ANALYSIS OF MIR-29B AND MIR-126 IN DIABETIC RETINOPATHY

MicroRNA and diabetes mellitus patients without retinopathy in escape room: Tournament of champions

Many miRNAs are involved in the occurrence and development of DR through various pathways. MiR-200b is sensitive to hypoxic environments and can regulate angiogenesis by controlling the expression of VEGF and the homologous 1 of bone marrow erythrocytosis virus E26 oncogene (Serocki *et al*., 2018; Sun *et al*., 2018). Sugar-induced oxidative stress can accelerate cell aging and promote fibronectin expression by regulating deacetylase in diabetic endothelial cells and the retina. Retinal apoptosis genes include MiR-29b and its potential target double-stranded RNA-dependent protein kinase binding protein X. MiR-29b may indirectly regulate the expression of RAX or inhibit retinal cell apoptosis by regulating the PKR signaling pathway, which also plays a vital role in the pathogenesis of DR (Soltani *et al*., 2020; Zhang *et al*., 2019). Other studies have shown that MiR-410 overexpressed in the model of oxygen-induced retinal neovascularization in rats can inhibit VEGF expression and reduce retinal neovascularization formation (Massart *et al*., 2017).

The course of diabetes and BMI are significantly related to the occurrence of NPDR, which mainly shows that the longer the course of diabetes and the higher the BMI, the higher the incidence of NPDR and proliferative diabetic retinopathy (PDR) (Kawasaki *et al*., 2019). PDR is a common and severe microvascular complication of T2DM, mainly due to long-term poor blood sugar control. Blood sugar permeates into the basement membrane of the eyes, forming a macromolecule polysaccharide that blocks capillaries, causing local ischemia, hypoxia, and inflammatory reaction, which leads to abnormal proliferation and fibrosis of retinal vessels' delicate cells, stimulating the formation of pathological new blood vessels (Kawasaki *et al*., 2019). After rupture and bleeding, it enters the vitreous body, causing fundus hemorrhage and blurring the patient's vision. Scar tissue will grow after vascular rupture, and pulling the retina will cause the retina to fall off, leading to complete vision loss. Our study establishes corresponding data maps to study interactions (Figs. 1 and 2).

Our study suggests that the retina of type 2 diabetes has a specific influence on miR-29, and the influence is as high as 54.42%. It was found that silencing the expression of miR-29c can inhibit the degree of renal

fibrosis in diabetic nephropathy rats through adenosine monophosphate-activated protein kinase/rapamycin target protein, suggesting that miR-29c is involved in renal fibrosis (Massart *et al*., 2017). Cell fibrosis is the primary pathological manifestation of DR, so the author speculated that miR-29c might participate in cell fibrosis and the occurrence of DR in some way. Studies have shown that the expression of miR-29c in the serum of DR patients is significantly increased, and it is speculated that the over-expression of miR-29c is involved in the occurrence of DR. The results of this study showed that the level of serum miR-29c in the control group, NDR group, and DR group gradually increased ($p < 0.05$), which was in line with the above research report, suggesting that miR-29c might be related to the occurrence of DR.

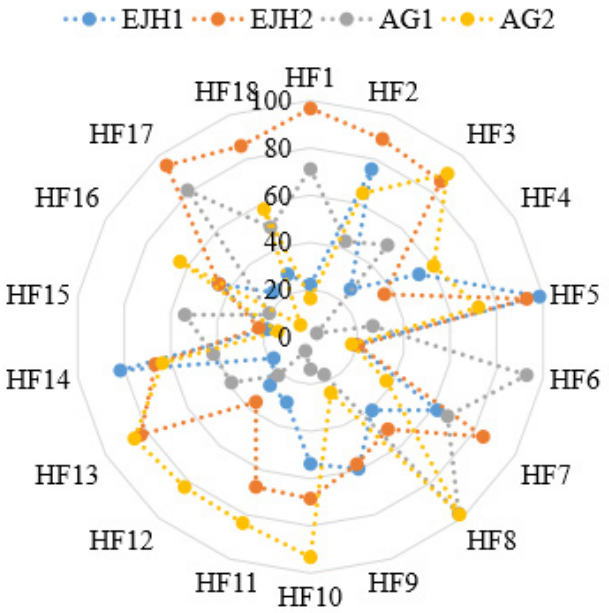

Fig. 1. Research analysis of relationships between EJH1, EJH2, AG1, AG2 and HF factors in 3mir-29 serum analysis.

Neovascularization refers to the newly protruding spiral capillaries. Its formation process includes the degradation of the basement membrane of vascular endothelial cells, the chemotaxis, proliferation, and migration of vascular endothelial cells, and the formation and maturation of neovascular cavities, among others. Vascular endothelial growth factor (VEGF) is a growth factor that can vigorously promote cell proliferation and differentiation. It can be synthesized by photoreceptor cells, pigment epithelial cells, and other retinal cells. It is the mitogen of retinal pigment epithelial cells and vascular endothelial cells. It can promote mitosis and chemotaxis of retinal pigment epithelial cells and vascular endothelial cells, induce vascular endothelial cells to produce various factors, destroy their basement membrane, and promote capillary endothelial cells to migrate to form collagen matrix, thus promoting the formation of new blood vessels.

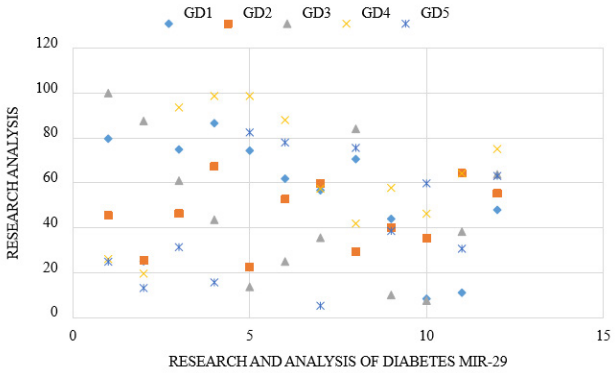

Fig. 2. Research analysis of expression levels of mir-29 based on GD1 to GD5 in the serum samples of patients.

Lipoprotein(a) (Lp(a)) is closely related to diabetic vascular complications, which is consistent with the related research results. Its mechanism is mainly that Lp(a) can promote the formation of atherosclerosis by competitively inhibiting the fibrinolytic function of plasminogen and its fibrinolytic activity of transforming growth factor (TGF-β). Therefore, Lp(a) can also cause retinal microvascular obstruction and microcirculation dysfunction, promote tissue ischemia and hypoxia, and finally lead to retinopathy. The results of this study showed that the Lp(a) level of the two groups was significantly different ($p < 0.01$). Multivariate analysis showed that the risk of NPDR in diabetic patients increased by 12% every time the Lp(a) level of diabetic patients increased by 1 mg/dL, which was consistent with the research results of Chopra and others in Kim Hye Yoon (Zhu *et al*., 2016) and Cho Jung Seok (Wang *et al*., 2018).

Analysis of MiR-126 in the retinas of patients with DR

The research on MiR-126 and diabetes focuses on its relationship with the pathogenesis and complications of type 2 diabetes mellitus (T2DM) (Venkat *et al*., 2019; Pordzik *et al*., 2021). The expression level miR-126 decreased in the standard control, impaired glucose tolerance (IGT), and T2DM groups. Systemic inflammation and oxidative stress caused by metabolic changes are the leading causes of cardiovascular complications in patients with type 1 diabetes mellitus (T1DM). Retinopathy is a common complication of diabetes that affects the eye's

retina (Park *et al*., 2021).

MiR-126 is involved in regulating the occurrence of inflammatory reactions. Kramp-Karrenbauer RP of HSC is a marker of elevated inflammation in diabetic patients. TG-rich lipoprotein in a high-fat diet can induce endothelial inflammatory reactions by regulating the expression of vascular cell adhesion molecule 1 (VCAM-1), among which the expression level of MiR-126 in individuals with an anti-inflammatory reaction is increased. It is speculated that MiR-126 is involved in the occurrence and development of diabetes by mediating the inflammatory reaction and causing the destruction of islet cells.

Endothelial function is a biomarker of macrovascular disease. Angiotensin II (Ang II) positively correlates with the inflammatory mediator MCP-1 (Devine *et al*., 2011). The specific mechanism may be that Ang II acts on endothelial cells through the integrin β1 signaling pathway, regulates the expression of Rho guanosine triphosphatase RAC1 in dendritic cells, stimulates nuclear translocation of NF-κB and degradation of NF-κB inhibitor IκB in vascular endothelial cells, and induces inflammatory cascade reactions in vascular endothelial cells, resulting in increased expression of inflammatory cytokines IL-1β, IL-6, and matrix metalloproteinase 9.

Ang II can act on monocytes to promote the expression of adhesion molecules, such as intercellular adhesion molecules and vascular cell adhesion molecules, and induce chemotaxis and inflammatory changes in monocytes (Park *et al*., 2021). The integrin signal pathway can modulate TLR4 signaling and participate in the innate immune response. The carboxyl-terminal of Ang II has a fibrinogen-like domain, and fibrinogen is the ligand of TLR4 in monocytes. Ang II may also function as a TLR4 ligand and participate in the occurrence and development of chronic low-grade inflammatory diseases (Figs. 3 and 4).

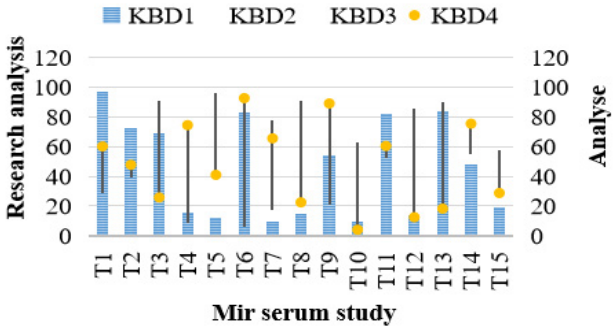

Fig. 3. Mir-126 analysis and the occurrence of DR in patients across T1 to T15 samples.

Figure 4 shows that serum MiR-126 has a strong influence and is related to DR in the context of Escape room: Tournament of champions, with an influence of approximately 53.64%. The expression level of MiR-126 was positively correlated with HDL cholesterol but negatively correlated with LDL cholesterol and total cholesterol. Multiple linear regression analysis suggested that LDL cholesterol was the influencing factor for MiR-126, that MiR-126 may be involved in cholesterol and fat metabolism, or that LDL cholesterol affected the expression of MiR-126.

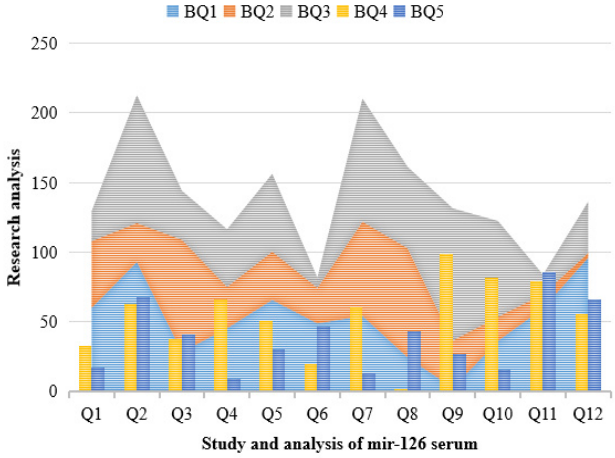

Fig. 4. A comparative analysis of mir-126 serum in patient samples from Q1 to Q12.

The expression of MiR-126 in plasma is low in patients with type 1 diabetes, and it is positively correlated with fasting C-peptide and 2-h C-peptide but has no correlation with fasting plasma glucose, postprandial glucose, and glycated hemoglobin. Multiple regression analysis suggested that fasting C-peptide was the influencing factor for MiR-126, indicating that the change in MiR-126 in type 1 diabetes patients might be related to islet function.

MiR-126 is a specific microRNA expressed in endothelial cells, and its decreased expression can mediate endothelial injury in diabetic patients (Devine *et al*., 2011). The mechanism of the injury may involve the reduction of biological activity of nitric oxide (NO) by inhibiting endothelial nitric oxide synthase (eNOS) or the activation of the nuclear factor kappa B (NF-κB) signaling pathway by decreasing the protein sulfhydryl nitrosation of p65, thus promoting inflammation and oxidative stress.

MiR-126 also regulates vascular inflammation and plays a protective role in atherosclerosis by inhibiting the expression of adhesion molecules such as VCAM-1. The inhibition of MiR-126 can promote the expression

of VCAM-1 and increase the adhesion of leukocytes to endothelial cells, which may reduce capillary formation, endothelial cell proliferation, and wound healing but promote endothelial cell-mediated angiogenesis.

CONCLUSIONS

The level of Lp(a) in peripheral blood can be affected by different races, genders, types of diabetes, and grades of retinopathy, which may contribute to differences among research results. In diabetic rats, nuclear factor-kappa B (NF-κB) expression was significantly increased in retinal endothelial cells (REC). As a critical regulator of immune inflammation, NF-κB plays an essential role in the early inflammatory response of DR. Whether *in vitro* or *in vivo*, NF-κB is activated in retinal endothelial cells in a high glucose environment and pericytes in a low oxygen environment, which leads to the upregulation of downstream inflammatory factors of NF-κB, such as intercellular adhesion molecule-1 (ICAM-1) and monocyte chemoattractant protein-1 (MCP-1).

Retinal apoptosis is another essential process involved in DR. Retinal apoptosis genes, such as MiR-29b and its potential target double-stranded RNA-dependent protein kinase (PKR) binding protein X, play an essential role in the pathogenesis of DR. Rax may be the direct activator of the PKR signaling pathway, which can activate the PKR signaling pathway and induce cell apoptosis in a stressful environment. Studies in normal and diabetic mice have shown that MiR-29b and Rax are located in retinal ganglion cells, and the retinal nuclear layer, and their expression increases in the early stages of diabetes.

MiR-29b may indirectly regulate the level of Rax and inhibit the apoptosis of retinal ganglion cells and the retinal nuclear layer cells through the PKR signaling pathway. These findings suggest that the dysregulation of MiR-29b and Rax and the activation of the NF-κB signaling pathway may contribute to the development and progression of DR.

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IRB approval

The study was approved by the Institutional Review Board of North China University (No.202261420).

Ethical statement

The study was approved by North China University Animal Ethics Committee(No.20230122897).

Statement of conflict of interest

The authors have declared no conflict of interest.

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