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REVIEW PAPER

Diabetic retinopathy: mechanisms, and upcoming biomarkers

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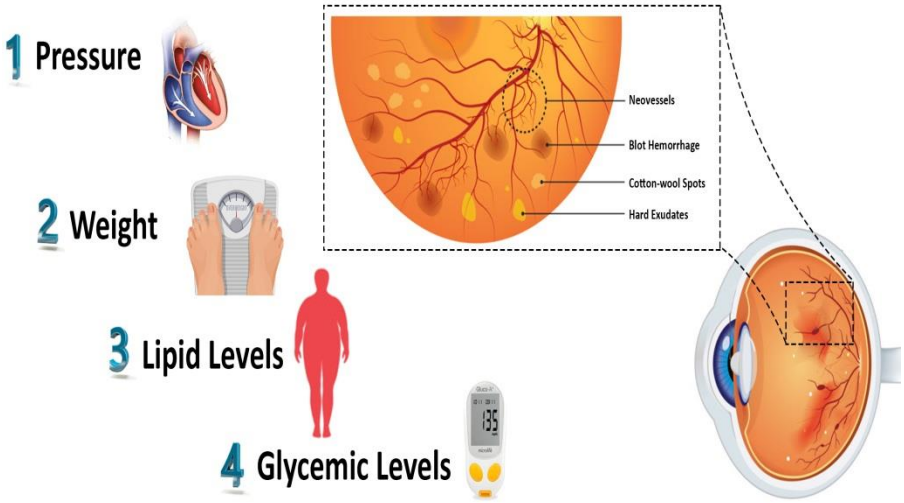
Highlights

- Risk of Diabetic retinopathy is closely linked to excessive TNF-a levels in the pediatric population.
- IL-6 is significantly correlated with macular edema incidence, an accelerated retinopathy marker in children with Diabetes and Diabetic retinopathy.
- miR146a, miR-200b, and miR-29b have been found to decrease Diabetic retinopathy.
- IP-10 and RANTES, as well as moderate diabetic retinopathy.
- A substantial increase in the level of IL-1a, IP-10, and MCP-2 was found in patients with either non-diabetic or early diabetic retinopathy.

Graphical Abstract



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Abstract

Obesity is an important issue that affects many people all over the world. This condition contributes to an increase in prevalence of type 2 diabetes. Furthermore, an unexplained rise in the number of type 1 diabetes has occurred. However, due to the recent developments in the field of diabetes care, it is still a significant cause of visual impairment in elderly. Diabetic retinopathy (D.R) is a critical issue for many people with diabetes. Various risk factors have been identified for diabetic retinopathy, including; blood pressure, weight, serum levels of lipid, and glycemic status. This pathology could be detected and treated by regular screening procedures, especially for late-stage of retinopathy. Angiogenesis inhibition is considered a modern therapy using intraocular steroids and intravitreal application of vascular endothelial growth factor (VEGF) treatments. Unfortunately, a majority of patients with diabetic retinopathy are unable to benefit from accessible medications. Diabetic retinopathy is more severe which require modern treatments. Discovering the molecular markers can increase the speed of research on D.R. Thus, there is a significant increase in diabetes and the urgent need for accurate detection of following diabetic retinopathy. Pathology can help in the detection of retinopathy in developing treatments and preventative methods for diabetic vision loss. This article discussed many important biomarker discoveries in these pathologic conditions.

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Introduction

D.R has a substantial financial burden on the healthcare services around the world (1). diabetes is predicted to be the most prevalent complication and rise from 4.15 million in 2015 to 6.4 million by the year 2040 (2-4). The presence of a significant global public health threat highlights the urgent need to explore new models of diabetes treatment (5-8). Todays, approved treatments are beneficial, but they also have serious side effects. Risk factors can be carefully followed in the early phases of the illness. Diabetes and blood pressure also are significant risk factors for developing D.R (7-9). There are no findings that glycemic regulation plays a crucial role in development and advancement of diabetes, but the research group found that to forecast up to 11% of the probability of developing diabetes and the remainder 89% due to system-wide features not reflected in HbA1c values (10, 11). As a result, more medical assays and monitoring are required for D.R medications. D.R is caused by medical, metabolic, and molecular influences as well as inherited conditions. This information described retinopathy and evaluated accepted and new techniques in biomarkers in this field.

Retinopathy stages

There are two stages of diabetic retinopathy; nonproliferative (NPD.R) and advanced proliferative (APD.R). NPD.R is characterized by microaneurysms, intraregional haemorrhage, venous beading, and intraregional microvascular defects. Although the NPD.R is often asymptomatic, it sometimes progresses to proliferative diabetic retinopathy if left untreated. NPD.R is sometimes associated with loss of visual acuity. PD.R is characterized by the formation of new arteries (neovascularization). It is believed to be triggered by retinal ischemia leading to release of growth factors such as VEGF (12). Bleeding through and out of defective fresh channels results in progression of fibro-vascular epi-retinal membranes, vitreous haemorrhage, and traction retinal isolation. Macular edema, the most dangerous complication of diabetes and the primary cause of vision loss which is correlated with diabetes, is another significant risk factor for D.R (13). Macular edema is classified as mild, moderate, or severe depending on the distance of exudates and thickness from the foveal nucleus (14).

Retina anatomy

The eye, which serves as the body's cortical matrix, comprises layers of neurons and glial cells and is supplied by a dense vascular network derived from the choroid and retinal arteries. Due to the retina's high metabolic activity, it is highly susceptible to ischemic insults. The retina is composed of photoreceptors with sensitivity to light signals in environment. These cells convert light signals to neuronal signals transmitted by the optic nerve to the brain’s visual cortex. Because the retina is the only neuronal tissue that is actively subjected to light, it is susceptible to photo-oxidized lipids, highly toxic to retinal cells (15). Two forms of photoreceptors in the retina are rods and cones, with cones responsible for color vision. Since the macula contains many cones, it is the most critical area of the eye for fine and color vision. Thus, slight macula damage (e.g., mild macular degeneration) may significantly impact visual acuity.

The cortical layer of the retina is made up of photoreceptors and sympathetic cells called glial cells, while the vascular layer is made up of the blood vessels that support the retina. Blood vessels in the retina exhibit unique characteristics that lead to the retina's normal growth. The most visible obstacle is the blood-retinal barrier (BRB), a strongly constrictive physiological barrier that controls the passage of molecules, proteins, and water into and out of the retina. The BRB is divided into two sections; inner BRB, which contains near junctions between retinal capillary endothelial cells, and the outer BRB, which contains tight junctions between retinal pigment epithelial cells. The BRB is necessary to preserve the eye's privileged location and allow for regular visual operation (16). Additionally, retinal blood vessels are unusual, owning a large concentration of pericytes, which are essential for preserving vascular integrity and regulation of endothelial proliferation (17).

Pathophysiology of D.R

Our existing knowledge of D.R. pathophysiology suggests that it is highly nuanced and multifactorial, requiring the activation of several interacting pathways that all lead to several critical mechanisms such as

increased levels of oxidative stress, proinflammatory mediators, and VEGF secretion. All of which occur in the context of the various metabolic Process. Additionally, diabetes impairs the role of neurotransmitters and neuroprotective factors throughout the retina. These events can destroy the synaptic and vascular systems of the retina, especially in D.R. pathology. Early in the disease's development, diabetes seems to impair normal regulatory processes in the retina's neurovascular complex, as shown by decreased vasoconstriction in response to 100% oxygen ventilation and decreased vasodilation response to a flashing light trigger (18).

Blood flow is natural, and the vascular configuration is stable in normal retinal vessels. However, in the retinopathy of diabetes, endothelial junctions are ruptured, pericyte ghosts are formed, basement membrane thickens, and further neovascularization occurs (Figure 1).

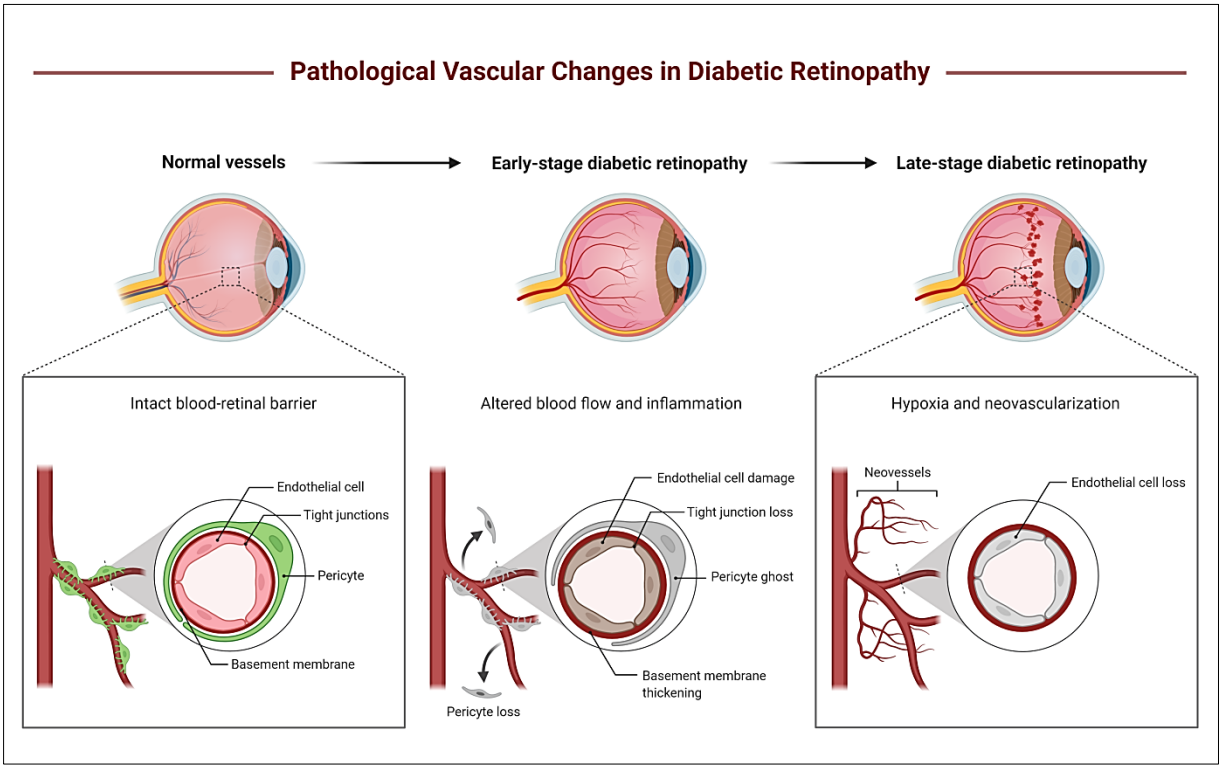

Figure 1. Blood flow is natural, and the vascular configuration is stable in normal retinal vessels. In the retinopathy following diabetes, the endothelial junctions are ruptured, pericyte ghosts are formed, the basement membrane thickens, and further neovascularization occurs.

According to the clinical data, the initial focus of D.R researches was on the vascular aspect; nevertheless, it has been shown that the early changes affect the whole neurovascular bundle, with functional weakness occurring in all components. There is already evidence that neuronal apoptosis occurs before apparent vascular abnormalities develop (19-22). Indeed, there is mounting evidence that neurodegeneration plays a role in the early microvascular changes seen in D.R., including BRB breakdown (via glutamate-mediated excitotoxicity, which promotes VEGF release), vaso-regression, and disrupted neurovascular connection (15). Damage to the BRB is an actual occurrence in D.R. The critical mechanism of the altered BRB behavior is a decreased trend in retinal cell permeability due to high growth factors, cytokines, advanced glycemic finishes, inflammation, hyperglycemia, and pericyte degradation (23). Retinopathy includes retinal microaneurysm, haemorrhages, and cotton-wool spots. The prominent characteristic of proliferative retinopathy is neovascularization, which is caused by retinal hypoxemia. Albeit the original and the ensuing effects are attributable to DM metabolic changes and elevated blood glucose, ischemic injury causes secondary neurological toxicity (Figure 2).

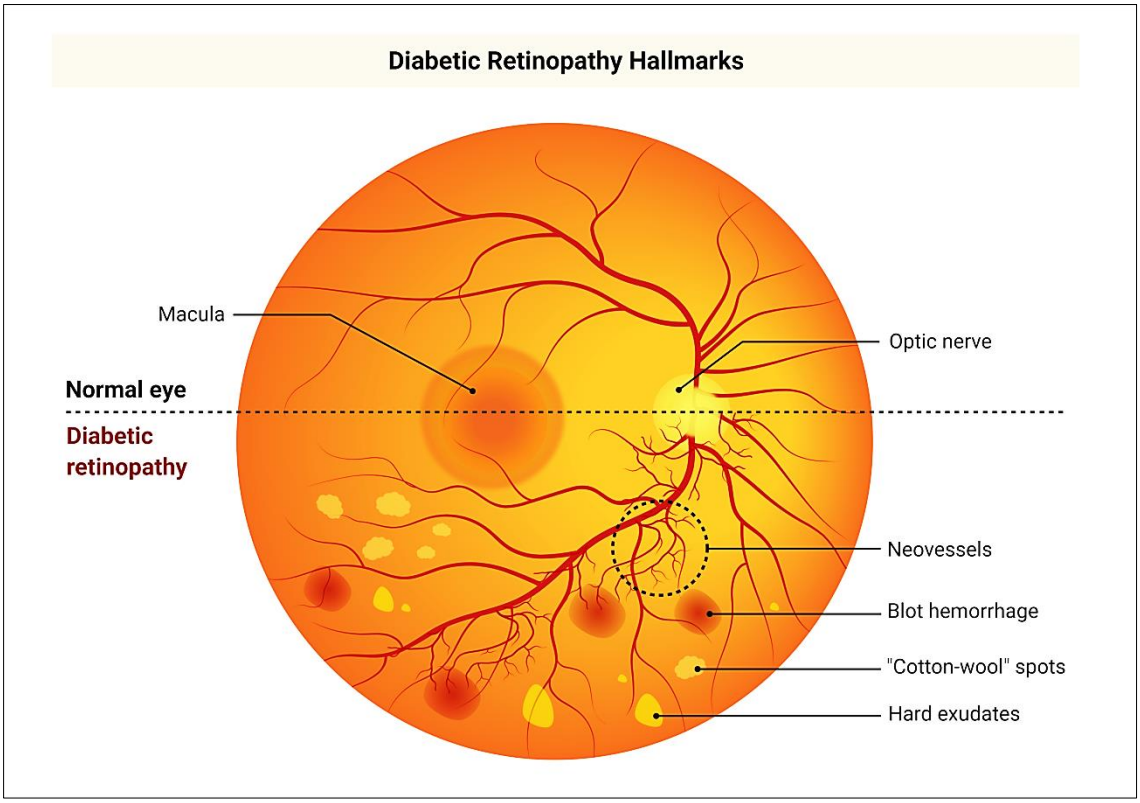

Figure 2. Retinopathy includes retinal microaneurysms, haemorrhages, and cotton-wool spots and characteristic of proliferative retinopathy is neovascularization which is caused by retinal hypoxemia.

Ischemia leads directly to neuronal injury and death, and tissue non-perfusion often causes several growth factors that encourage angiogenesis, which is the distinguishing feature of PD.R. With various levels of cross-conversation between the related elements is impossible to distinguish any case from any other. Furthermore, new causes that continue to be identified influence D.R. pathogens seem to have a wide variety of seriousness of microvascular symptoms, including in diabetic patients with similar biochemical profiling. Cunha-Vaz et al., (2014) proposed three distinct D.R phenotypes known as A, B, and C with the slow-progress form A, while B and C with high leakage levels and C with the capiller's closure symbol (13). The processes that influenced the potential predominance of distinct pathways in distinct phenotypes remain unknown. The risk of D.R is contributed by clinical, biochemical, and molecular influences, including genetic and epigenetic factors. Many considerations also have a therapeutic focus, and some could be potential therapeutic agents, including microRNAs (4). Traditional and new biomarkers knowledge will increase prognosis and formulate and personalize primary and secondary retinopathy preventive strategies. Also, the majority of biomarkers identified to date are focused on the evaluation of molecules underlying the pathogenesis of D.R, which most important are inflammation and angiogenesis.

Inflammatory Biomarkers

1. Circulating Cytokines

Many inflammatory molecules have been proposed as serum biomarkers of D.R, especially TNF-a (24). TNF-a is a cytokine that allows leucocytes to permanently bind to the endothelium (leukostasis) and increase the synthesis of the reactive oxygen species (25, 26). Also, a strong connection between plasma TNF-a and PD.R levels was identified (27, 28). Klein et al., stated that the involvement of kidney disease causes this correlation (29). TNFa levels at baseline were predictive of D.R incidence and development of diabetic complications (30, 31). The risk of D.R was closely linked to excessive TNF-a levels in the pediatric population discovered by Zorena (32). Moreover, the level of TNF-a in tears is correlated with D.R (33). Currently, elevated levels of TNF-a have been found in Serum and A.H. in DME patients, but not in non-diseased Serum (34). Studies of I.L. levels

in the vitreous fluid were associated with diabetic retinopathy, which has led to the idea that they play a significant role in the disease's development (35, 36).

Shimizu et al., have found that serum IL-6 is significantly correlated with macular edema incidence and can be a PD.R marker in children with Diabetes and D.R (27, 37-39). Diabetic patients had a higher z-score than control subjects that were found to be associated with C-reactive protein, TNF-a, and IL-6 levels. The researchers discovered a close connection between these proinflammatory conditions. They typed two diabetes, diabetic nephropathy, and cardiovascular disease (40).

2. Retinol-Binding Protein 4

RBP4 as a vitamin is a transport protein secreted by hepatocytes and adipose tissue (41). Research has shown that RBP4 levels in the blood are correlated with BMI, waist-to-hip ratio, triglyceride levels and systolic blood pressure. These are all part of the metabolic syndrome. It has been hypothesized that increased RBP4 concentrations could contribute to insulin resistance in individuals who are obese, with type 2 diabetes, or glucose intolerance (42). These researchers have discovered that due to over-expression of RBP4, there was an early onset of microglia activation with ongoing retina degeneration in an animal model induced by increased production of proinflammatory cytokine IL-18. Thus, the RBP4 enzyme may be implicated in the inflammatory response used to determine the early stages of the disease (43).

Takebayashi et al. discovered that the levels of RBP4 were elevated in patients with type 2 diabetes mellitus, but this lost significance after controlling for urine albumin excretion (ABE) (44). Moreover, the Li et al., discovered that the UAE and serum RBP4 concentrations were also significantly elevated in patients with primary bladder cancer. However, many other studies found no correlation between RBP4 levels and depression (43, 44). Numerous factors, like BMI, some D.Rugs, vitamin A deficiency, and GFR, may influence RBP4 levels. Additional research to clarify these confounding variables is necessary (41-44).

In patients with T2DM, there is a low degree of systemic inflammation, and both adipose and macrophages mainly cause production of proinflammatory cytokines. Plasma diffusion can contribute to the development and progression of D.R by breaking down the blood-retinal barrier, but proinflammatory cytokines/chemokines can be primarily caused by locale synthesis. Thus, RPE and glial cells (macroglial cells and microglial), which release proinflammatory cytokines, are vital for D.R pathogenesis (45).

Inflammatory regional Biomarkers

Muller cells are the retina's primary macroglia cells and are thought to connect vessels and neurons, controlling neuronal nutrition, development, and metabolism (46). Muller cells control the homeostasis of potassium and water, in addition to their crucial role in the supportive and signalling neuronal in the structure and photopigment process, preserve the integrity of the blood-retinal barrier and participate with the release of neuroinflammatory and vasoactive mediators in local retinal inflammatory reactions. Muller cells respond to hyperglycemia through reactive glycosides characterized by increased glial, nestin, and vimentin fibrillary acid protein, as well as functional activation and cell proliferation (47).

In laboratory research and diabetic donors, there has been an increase in GFAP levels (48-53). A raised GFAP in human ocular fluids has been found in people with diabetes who are nonproliferative or have nonproliferative D.R, regardless of their symptoms (54). Additionally, it has been found that an increase in AQP4 (a membrane channel protein that allows water to pass) has been observed in animals with diabetes. More recently, an increase in AQP4 was noted in patients with no evidence of D.R in the eye (54). The A.H. biomarkers of Muller cell could be regarded as AGFAP and AQP4 (activation). Activation in D.R. retinal microglial cells has been verified in clinical experiments with optical coherence tomography (OCT) (55-59), microglia (microglia) is the primary immune cell type, and central nervous system cells express similar levels of monocyte and macrophage markers (60, 61). Microglia cells in D.M alter the phenotype of their activity and migrate from inside to outside retinal cells (62-64). Multiple signals and modulators can induce (alerted and

reactive) microglial cell activation, including supplementation; antibodies; cytokines; chemical elements; viral, bacterial, or fungal DNA/RNA, endogenic abnormal proteins, plasma components, proteins, peptides, and nerve-transmission-related compounds and ions (65).

A general number of proinflammatory cytokines produced by retinal glial cells were seen in the A.H. recently (66). A substantial increase in the level of IL-1a, IP-10, and MCP-2 was found in patients with either non-diabetic or early diabetic retinopathy. In contrast, IP-10 and RANTES, as well as moderate diabetic retinopathy, were elevated in patients with D.R.; the levels of diabetic patients with any degree of inflammation showed a rise in inflammatory protein (GM-SF, RANTES, TNFA-II) had a significantly elevated level (66). When the D.R progressed to a higher degree, e.g., with increased concentration, the following cytokines were identified in A.H; DME or proliferative D.R, IL- 6, VEGF, IL-12, IL-8, IP-10. There was a rise in PDGF in the vitreous fluid, whereas (platelet-derived growth factor) and intercellular adhesion molecule (ICAM-1) concentrations (67-70). While vitreous fluid can more accurately represent pathophysiological events in the retina than A.H., its sampling is considered too invasive to be used in hospital procedures, except for some patients' vitrectomy applicants (71).

Hemopexin

Hemopexin has been involved in inflammation, apart from proinflammatory cytokines. Diabetic retinopathy has been observed to have exaggerated expression, and in vitro experiments have shown that the blood-retinal barrier has become permeable. The impact was detected at hemopexin concentrations comparable to those seen in the vitreous fluid of DME patients (50l g/mL) (72). We are convinced that Hemopexinis the most extensively characterized compoundable factor in the human body. High levels of premium in the urine causes the nephrotic syndrome, which is accelerated by uremic factors in the body (73). Additionally, Hemopexin increases or helps maintain the glomerular capillaries' permeability in Minke-type changes (74).

In vitro, T-cell cytokines such as TNF-a have been shown to increase the development of hemopexin in mesangial cells, which are inhibited by Corticosteroids (73, 75). It may also be that the increase in hemopexin due to diabetes has an equally similar impact on the retina, which leads to the primary pathogenic factor, DME, vascular leakage (hyperpermeability). Indeed, dexamethasone significantly reduced the hyperpermeability caused by hemopexin (76).

Circulating RNA

Nucleic acids have been found in peripheral blood, establishing a new diagnostic and prognostic method. The concentration of plasma nucleic acids (DNA and RNA) has been hypothesized to represent the degree of cell death. Indeed, they are increased in various pathological systems, including a variety of cancers (77).

mRNA

Hamaoui et al., examined rhodopsin messenger RNA levels in plasma samples from diabetic patients with different levels of D.R (77). Rhodopsin is a visual pigment found primarily in the retina's rod cells (78), and it has been observed in the peripheral blood of healthy individuals and diabetic patients with and without D.R. During the more severe stages of retinopathy, the levels of rhodopsin expression tended to rise. In the PD.R population, there were no significant variations between these patients and control group of healthy individuals (79). In an additional analysis, mRNA from rhodopsin and mRNA from retinal amine oxidase are combined, a protein that is also expressed exclusively in the retina, which decreases with the developmental progression of D.R, and the ratio between them is determined. The curve was significantly higher than rhodopsin only so that they could tell the difference between moderate and severe D.R (80), mRNA circulating levels of RPE65, and retinoschisis, both of which are unique to the retina, are additional potential biomarkers. Shalchi et al., demonstrated that circulating RPE65 mRNA levels increase with the intensity of D.R., while plasma **Retinoschisin** mRNA levels decrease (80). Several scientific studies have uncovered the mechanisms that lead

to the possible upregulation of RPE65 and retinoschisis messenger levels in degeneration in severe conditions, especially in the effective loss of RPE65 and retinopathy age-related macular cell death (78, 81). However, It should be noted that the mRNA was found in both healthy and patients with diabetic retinopathy. Longitudinal studies may therefore help explore the function of D.R predictors.

miRNA

MicroRNAs (miRNAs), ecologically generated short coding RNAs, have a role to play in modulating gene expression via post-transcriptional pathways of approximately 20–22 nucleotides and inhibit their target genes' expression (82, 83, 84). Because of their consistency in blood and urine and the fact that they are tissue-specific, miRNAs are excellent biomarkers for the early diagnosis of D.R. Several miRNAs have emerged in recent years as relevant regulators of D.R pathology (85, 86, 87). Besides, some species-specific miRNAs (such as miR146a, miR-200b, and miR-29b) have decreased in animals, such as VEGF and PAX. The decrease in these miRNAs is associated with an increase in the corresponding proteins in D.R (88, 89, 90). Recently, Hernández et al., examined the expression of miR-126 in endothelial progenitor cells and found it to be higher in patients with diabetes (71, 91). However, there is strong evidence to suggest that the tide of miRNA research is rapidly growing, but as noninvasive biomarkers and even possible therapeutic targets remain unclear.

Concluion

Despite progress in medicine and an increasing number of therapies for diabetic retinopathy, at least in developed countries, sight loss from the disease is still the principal and feared complication of diabetes. Diabetic retinopathy is one of the world's major causes of blindness, and with the increasing number of people at risk, the problem is only going to become more acute. Biomarkers are now commonly used and helped to develop treatment options in both clinical and clinical science. However, we cannot predict who would experience diabetic retinopathy, nor do we know whether it is treatable with standard methods. Both therapies have possible side effects, which are detectable by biomarkers. Advances in clinical, biochemical, and molecular testing can lead to more clinical science and practice advances. Thus, additional biomarker research is essential to advance our understanding of diabetic retinopathy and its clinical outcomes. Pre-analysis, pre-diagnostic, analytic, and post-analytic criteria help reduce the incidence of diabetic retinopathy.

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