Diabetic Retinopathy: An Overview on Pathophysiology, Diagnosis and Recent Advances in the Treatment

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ABSTRACT:

Diabetic Retinopathy (DR) is the condition caused due to uncontrolled diabetes that can lead to vision impairment. It greatly affects the retinal blood vessels and diminishes the fundus light-sensitive inner coating. Early diagnosis and regular screening of this disease are essential for prompt processing through artificial intelligence techniques. This paper targets assessing the latest techniques for screening and diagnosing DR, including 94 articles based on the Detection and grading of DR. Diabetic retinopathy, a leading cause of vision loss in working-age adults, is a complication of diabetes mellitus where damage to the retina's blood vessels occurs, potentially leading to blindness if left untreated. Diabetic retinopathy the most frequently occurring complication of diabetes mellitus and remains a leading cause of vision loss globally. The manual diagnosis process of DR retina fundus images by ophthalmologists is time-, effort, and cost-consuming and prone to misdiagnosis unlike computer-aided diagnosis systems. Recently, deep learning has become one of the most common techniques that has achieved better performance in many areas, especially in medical image analysis and classification. Variation in compliance rates, age of onset of diabetes, glycaemic control and screening sensitivities influence the cost-effectiveness of screening programmes and are important sources of uncertainty in relation to the issue of optimal screening intervals.

KEY WORDS: Diabetic Retinopathy, Insulin, fluorescein angiography, vitreous haemorrhage.

INTRODUCTION:

The inability of the body to manage the generated insulin leads to diabetes. There are two categories of diabetes, particularly type 1 and type 2 diabetes. Type 1 diabetes is inevitable, and the cause is not known while type 2 diabetes can be diagnosed by the symptoms present in retinal images. Type II diabetes can be detected by diverse symptoms such as microaneurysms (MAs), Haemorrhages (HEMs), exudates (EXs), cotton wool spots (CWs), etc. When left untreated for more than 5 years and above, it can lead to Diabetic Retinopathy (DR) in ophthalmology.

The purpose of this work was to provide a brief overview of diverse imaging modalities, datasets, and the literature behind detecting the lesions for diagnosing diabetic retinopathy. Background diabetic retinopathy. Probably percent of eyes afflicted with diabetic retinopathy have only this mild form of the disease, background or no proliferative retinopathy, although all diabetic retinopathy starts this way. These eyes will have good visual function unless there is some ophthalmic problem other than the retinopathy.

The clinical course of background retinopathy is quite variable. The retinal vascular abnormalities are constantly changing with a reabsorption of the haemorrhages and exudates, while at the same time new abnormalities are developing. There may be almost complete clearing of background changes, or they may progress to the point of causing a loss of visual function. The eyes should be observed on a regular basis so that treatment can be given when indicated. : The best way to diagnose diabetic retinopathy is a dilated eye exam. During this exam, the physician places drops in the eyes to make the pupils dilate (open widely) to allow a better view of the inside of the eye, especially the retinal tissue. The physician will look for:

• Swelling in the retina that threatens vision (diabetic macular edema)

• Evidence of poor retina blood vessel circulation (retinal ischemia pronounced is KEY me uh)

• Abnormal blood vessels that may predict an increased risk of developing new blood vessels

The primary cause of diabetic retinopathy is diabetes a condition in which the levels of glucose (sugar) in the blood are too high. Elevated sugar levels from diabetes can damage the small blood vessels that nourish the retina and may, in some cases, block them completely. When damaged blood vessels leak fluid into the retina it results in a condition known as diabetic macular edema which causes swelling in the centre part of the eye (macula) that provides the sharp vision needed for reading and recognizing of faces.

PATHOPHYSIOLOGY:

DIABETES

Diabetes is a disease that occurs when your blood glucose, also called blood sugar, is too high. Glucose is your body's main source of energy. Your body can make glucose, but glucose also comes from the food you eat.

Insulin is a hormone made by the pancreas that helps glucose get into your cells to be used for energy. If you have diabetes, your body doesn't make enough or any insulin, or doesn't use insulin properly. Glucose then stays in your blood and doesn't reach your cells.

Diabetes raises the risk for damage to the eyes, kidneys, nerves, and heart. Diabetes is also linked to some types of cancer. Taking steps to prevent or manage diabetes may lower your risk of developing diabetes health problems.

View full-sized image. On the left, a diagram of a blood vessel that has a normal blood glucose level and contains fewer glucose molecules. On the right, a diagram of a blood vessel that has a high blood glucose level and contains more glucose molecules.

Diabetes is a disease that occurs when your blood glucose, also called blood sugar, is too high.

What are the different types of diabetes?

The most common types of diabetes are type 1, type 2, and gestational diabetes.

Type 1 diabetes

If you have type 1 diabetes, your body makes little or no insulin. Your immune system attacks and destroys the cells in your pancreas that make insulin. Type 1 diabetes is usually diagnosed in children and young adults, although it can appear at any age. People with type 1 diabetes need to take insulin every day to stay alive.

Type 2 diabetes

If you have type 2 diabetes, the cells in your body don't use insulin properly. The pancreas may be making insulin but is not making enough insulin to keep your blood glucose level in the normal range. Type 2 diabetes is the most common type of diabetes. You are more likely to develop type 2 diabetes if you have risk factors, such as overweight or obesity, and a family history of the disease. You can develop type 2 diabetes at any age, even during childhood you can help delay or prevent type 2 diabetes by knowing the risk factors and taking steps toward a healthier lifestyle, such as losing weight or preventing weight gain.

Gestational diabetes

Gestational diabetes is a type of diabetes that develops during pregnancy. Most of the time, this type of diabetes goes away after the baby is born. However, if you've had gestational diabetes, you have a higher chance of developing type 2 diabetes later in life. Sometimes diabetes diagnosed during pregnancy is type 2 diabetes

DIABETIC RETINOPATHY

Diabetic retinopathy is an eye condition that can cause vision loss and blindness in people who have diabetes. It affects blood vessels in the retina (the light-sensitive layer of tissue in the back of your eye).

If you have diabetes, it's important to get a comprehensive dilated eye exam at least once a year. Diabetic retinopathy may not have any symptoms at first but finding it early can help you take steps to protect your vision.

Managing your diabetes by staying physically active, eating healthy, and taking your medicine can also help you prevent or delay vision loss. Other types of diabetic eye disease.

Diabetic retinopathy is the most common cause of vision loss for people with diabetes. But diabetes can also make you more likely to develop several other eye conditions:

Cataracts. Having diabetes makes you 2 to 5 times more likely to develop cataracts. It also makes you more likely to get them at a younger age. Learn more about cataracts.

Open-angle glaucoma. Having diabetes nearly doubles your risk of developing a type of glaucoma called open-angle glaucoma. Learn more about glaucoma. Diabetic retinopathy is the leading cause of visual loss in adults of the working-age group in the western population. It is the most common microvascular complication of diabetes mellitus. Diabetic retinopathy may lead to vision-threatening damage to the retina, eventually leading to blindness. Strict glycemic control, early detection, and appropriate management is the key to halting the progression of the disease. This activity reviews the pathogenesis, diagnosis, and management of diabetic retinopathy and highlights the role of the interprofessional team in evaluating and treating patients with this condition.

Objectives:

Describe the etiology of diabetic retinopathy.

Summarize the clinical features that will present in an evaluation of diabetic retinopathy.

Review the management and prognosis of diabetic retinopathy.

Highlight the role of interprofessional collaboration in improving the outcomes in patients with diabetic retinopathy.

HISTORY

Natural History of Diabetic Retinopathy

Diabetic retinopathy progresses from mild non-proliferative abnormalities, characterized by increased vascular permeability, to moderate and severe non- proliferative diabetic retinopathy (NPDR), characterized by vascular closure, to proliferative diabetic retinopathy (PDR), characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous. Macular edema, characterized by retinal thickening from leaky blood vessels, can develop at all stages of retinopathy. Pregnancy, puberty, blood glucose control, hypertension, and cataract surgery can accelerate these changes. Vision-threatening retinopathy is rare in type 1 diabetic patients in the first 3–5 years of diabetes or before puberty. During the next two decades, nearly all type 1 diabetic patients develop retinopathy. Up to 21% of patients with type 2 diabetes have retinopathy at the time of first diagnosis of diabetes, and most develop some degree of retinopathy over time. Vision loss due to diabetic retinopathy results from several mechanisms. Central vision may be impaired by macular edema or capillary nonperfusion. New blood vessels of PDR and contraction of the accompanying fibrous tissue can distort the retina and lead to tractional retinal detachment, producing severe and often irreversible vision loss. In addition, the new blood vessels may bleed, adding the further complication of preretinal or vitreous haemorrhage. Finally, neovascular glaucoma associated with PDR can be a cause of visual loss.

CAUSES:

Diabetic retinopathy is caused by prolonged high blood glucose damaging the small blood vessels of the retina, though the mechanism by which this occurs is unknown. Progression of diabetic retinopathy is accompanied by loss of capillary cells, increased blood vessel permeability in the retina, and altered retinal blood flow, all of which can reduce the amount of blood oxygen that gets delivered to the retina. Poor oxygenation of tissues drives the formation of new blood vessels throughout the retina, resulting in the proliferative stage of disease. These new blood vessels tend to rupture easily, causing bleeding within the eye, scarring, and damage to the retina or macula. Recent evidences have found a strong association between diabetic retinopathy and inflammation.

Diabetic retinopathy is an eye disease caused by diabetes. Diabetes can affect your eye care, making it especially important to get a regular eye exam. Damaged blood vessels and abnormal new ones can cause vision loss.

SYMPTOMES:

SYMPTOMS OF DIABETIC RETINOPATHY

As the condition progresses, diabetic retinopathy

symptoms may include:

Spots or dark strings floating in your vision (floaters)

Blurred vision

Fluctuating vision

Dark or empty areas in your vision

Vision loss

Difficulty with color perception

Diabetic retinopathy usually affects both eyes.

Diabetic retinopathy may be classified as early or advanced, depending on your signs and symptoms.

Early diabetic retinopathy. This type of diabetic retinopathy is called nonproliferative diabetic retinopathy (NPDR). It's called that because at this point, new blood vessels aren't growing (proliferating). NPDR can be described as mild, moderate or severe. When you have NPDR, the walls of the blood vessels in your retina weaken. Tiny bulges (called microaneurysms) protrude from the vessel walls, sometimes leaking or oozing fluid and blood into the retina. As the condition progresses, the smaller vessels may close and the larger retinal vessels may begin to dilate and become irregular in diameter. Nerve fibers in the retina may begin to swell. Sometimes the central part of the retina (macula) begins to swell, too. This is known as macular edema. Advanced diabetic retinopathy. Proliferative diabetic retinopathy (PDR) is the most severe type of diabetic retinopathy. It's called proliferative because at this stage, new blood vessels begin to grow in the retina. These new blood vessels are abnormal.leak into the clear, jelly-like substance that fills the center of your eye (vitreous). Eventually, scartissue stimulated by the growth of new blood vessels may cause the retina to detach from the back of your eye. If the new blood vessels interfere with the normal flow of fluid out of the eye, pressure may build up in the eyeball, causing glaucoma. This can damage the nerve that carries images from your eye to your brain (optic nerve). Diabetic retinopathy can happen to anyone who has diabetes. These factors can increase your risk:

Duration of diabetes the longer you have diabetes, the greater your risk of diabetic

retinopathy

□ Poor control of your blood sugar level

□ High blood pressure

□ High cholesterol

□ Pregnancy

□ Tobacco use

DIAGNOSIS:

Diagnosis and Management of Diabetic Retinopathy

Diabetic patients, along with their relatives, friends, and healthcare providers, must be informed about the significance of regular eye examinations to check for DR early .Diabetology 2022, Some of the diagnostic techniques that may be used

to diagnose, identify, and examine DR, as well as the efficacy of treatment, are direct and indirect ophthalmoscopy, stereoscopic digital and Fundus photography, mydriatic or nonmydriatic digital color or monochromatic single-field photography, ultrawide-field fundus fluorescein angiography (UWFA), optic coherence tomography (OCT), and optic coherence tomography-angiography (OCT-A), as well as fluorescein angiography. The most common method of diagnosis of diabetic retinopathy is ophthalmoscopy. However, compared to stereoscopic seven-field color photography, un-dilated ophthalmoscopy has low sensitivity, especially when performed by practitioners not involved with eye care. Direct ophthalmoscopy, when performed bynon-ophthalmologists, can detect approximately 50% of cases of proliferative retinopathy under normal clinical situations . The Early Treatment Diabetic Retinopathy Study(ETDRS) group certified the grading of stereoscopic color fundus photographs in seven standard fields (SSFs) as a recognized standard for the diagnosis of DR. Although this method is precise and repeatable, it requires the use of professional photographers and photo readers, as well as advanced photographic equipment, film processing, and archiving. A diabetic retinopathy diagnosis methodology on the basis of single-field fundus photography has also been used. Patients with type 1 or type 2 diabetes were photograph consecutively through a non-pharmacologically dilated pupil using single-field digital monochromatic non-mydriatic photography (SNMDP), and then pharmacologically dilated before being examined by an ophthalmologist using ophthalmoscopy and having 30◦color stereoscopic photographs taken in SSFs. However, comparative studies that were well planned have shown that single-field fundus photography may be used as an early diagnostic technique for diabetic retinopathy, detecting individuals with retinopathy and recommending them for ophthalmic diagnosis and care . The ETDRS group introduced the standard seven-field stereoscopic fundus photographs for diagnosis of the severity of diabetic retinopathy . Fundus photography was used to obtain a new record; therefore, it is recommended methodology for evaluating retinopathy . One of the most not able developments in the last decade has been the increasing use of ultrawide-field fundus fluorescein angiography (UWFA) and OCT in DR for diagnosis. The UWFA captures upto 200◦ of the peripheral retinas in just one frame. According to recent research, it can be used to view 3.2-times the amount of retinal surface area in contrast to the conventional seven standard fields. In comparison to the typical seven standard fields, UWFA was found to image 3.9 times more nonperfusion, 1.9 times more neovascularization, and 3.8times more pan-retinal photocoagulation. Its utilization for better imaging of the retinal periphery may have significant implications for the management of DR in patients .Moreover, in the diagnosis of DR, fluorescein angiography and OCT are even used by ophthalmologists to examine the permeability (leakage) and thickness of the blood vessels in the retina. Advanced technologies, such as OCT angiography, are also growing in popularity . Since its emergence, OCT has transformed clinical imaging for assessment and disease control in most retinal disorders, including DME . It is a non-invasive imaging method for obtaining high-resolution cross-sectional pictures of the retina, the retinal nerve fibre layer, and the optic nerve head . The current third-generation optic coherence tomography (OCT) technology utilizes a swept-source (SS) light source to produce three-dimensional raster photographs with a great microstructural resolution, commonly known as optical histology . Optical coherence tomography angiography(OCT-A), a recent advancement, has revolutionized the ability of professionals to investigate the complex vasculature of the retina without the usage of a contrast dye . OCT-Ais a non-invasive diagnostic technique that generates images that resemble angiographic pictures using motion contrast imaging. It produces a very detailed view of the retina vasculature, allowing accurate delineation of the foveal avascular zone (FAZ) and the diagnosis of minor microvascular anomalies such as extension, capillary non-perfusion areas, and intraretinal cystic spaces. The capability to detect microvascular alterations in diabetic eyes prior to the appearance of apparent microaneurysms might have far-reaching ramifications in the future . Fluorescein angiography is an invasive, expensive, and Diabetology 2022, 168time-consuming procedure for detecting vascular changes caused by the rupture of the inner and outer blood–retinal barrier in DR. However, the retinal vasculature may be seen with great precision, allowing the examiner to spot small microaneurysms and distinguish between them (hyperfluorescent) and punctiform haemorrhages (hypo-fluorescence due to the masking effect). It is an indispensable investigation before deciding on laser therapy, such as, to distinguish ischemic retinal edema from leakage, which turns white following the accumulation of dye (hypo-fluorescent). The use of laser effects in this circumstance is not suggested since it increases retinal ischemia.

TRADITIONAL MEDICATION

Traditional Chinese medicine in treatment

1. Prescriptions

Clinical studies have confirmed that TCM prescriptions exhibit significant effects in the treatment of DR . In the process of DR, a variety of endogenous and exogenous factors can cause inflammation, oxidative stress, angiogenesis and cell apoptosis in the eyes . Therefore, clinical practices mainly focus on the TCM prescriptions with the effects of eliminating ocular heat syndromes, activating blood circulation and removing blood stasis, as well replenishing Qi . Interestingly, Danhong Huayu Koufuye can inhibit the inflammatory and oxidative stress responses of DR . The proinflammatory TNF-α has been demonstrated to be involved in a variety of intraocular inflammatory diseases . Amazingly, Li et al. found that Mimeng flower decoction could ameliorate DR by down-regulating the network hub gene of TNF-α .

The involved mechanisms maybe related to inhibit the expression of caspase-3, MMP-2/9, and the accumulation of carbohydrate macro molecule. Recently, an increasing number of studies have demonstrated that SOCS3 can negatively regulate the STAT3 pathway, contributing to inflammation, apoptosis, and insulin signaling in hyperglycaemia-stimulated retinal endothelial cells . However, Huoxue Jiedu formula (HXJD) could inhibit HG-induced apoptosis and SOCS3/STAT3-induced VEGF overexpression and inflammatory response in DR rats . As broad-spectrum protease inhibitors, increased proteins expression of TIMP1 and A2M in patients and animals with DR can irreversibly inactivate MMP-2/9 and regulate the ratio of TIMPs/MMPs . While HXJD might impede the progress of DR through the inhibition of the TIMP1-A2M evoked apoptosis

2. Herbals

Clinical and in vitro and in vivo experiments also confirmed that the herbs and its extract had significant effects in the treatment of DR . The hyperglycemia induced inflammation has been considered as a risk factor for retinopathy, such as vascular defects, BRB damage and increased retinal vascular permeability . Lycium barbarum polysaccharides could exert the protective effects on BRB by regulating the Rho/ROCK inflammatory signaling pathway in diabetic rats . As an omega-3 (ω3) fatty acid receptor, the ubiquitously expressed G protein-coupled receptor 120 (GPR120) was extensively demonstrated to contribute to DR by its anti-inflammatory properties

In addition to inflammatory cascade, the retinal ischaemia and hypoxia can initiate angiogenesis in DR . Liang et al. confirmed that the root extract of Stephania tetrandra S. Moore could suppress capillary regeneration of posterior ocular region in DR rats through the activation of tetrandrine . Moreover, accumulating pieces of evidence suggested that hypoxia-activated HIF-1α-VEGF signaling pathway could damage the structure of BRB via promoting retinal angiogenesis in DR . Furthermore, Vaccinium myrtillus, Lonicerae japonicae Flos, Abelmoschus Manihot and total lignans from Fructus Arctii were demonstrated to inhibit the angiogenesis of DR by enhancing the VEGF expression

3. Identified compounds

In recent years, increasing scholars have extracted extensive monomer compounds from TCM to treat DR. Therefore, we summarized and further analyzed the related molecular mechanisms. The molecular formulae of 22 compounds and the involved mechanisms are shown in Sesamin could be of therapeutic benefit in slowing the progression of DR by ameliorating hyperglycemia-induced inflammation . Interestingly, trans resveratrol could ameliorate retinal inflammation through repression of NF-κB and ERK1/2 signaling pathways

Tzeng Thing-Fong er al further suggested that the protective effect of zerumbone on retina might be associated with the blockade of the AGEs/RAGE/NF-κB pathway . Inflammation induced overexpression of MMP-2/9 had been shown to aggravate the damage of DR . Coincidently, paeoniflorin could suppress HG-induced MMP-9 expression in retinal microglia via inhibition of the TLR4/NF-κB pathway . The anti-DR effects of some other compounds were also related to the inhibition of microglia inflammation-triggered BRB breakdown, such as galangin and scutellarin

MEDICINAL TREATMENT

Glycemic control At present, the most effective medical treatment to slow the progression of diabetic retinopathy is glycemic control. The relationship between hyperglycemia and retinopathy has been reported in well conducted observational studies . The Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS) are two randomized clinical trials that conclusively showed the efficacy of glycemic control in preventing

diabetic retinopathy . The DCCT investigated whether intensive treatment of glycemia would prevent or delay the progression of early NPDR (primary prevention) and whether intensive glycemic control would prevent the progression of early retinopathy to more advanced forms of retinopathy (secondary intervention) (1). Patients eligible for the primary prevention cohort had type 1 diabetes for 1–5 years and no retinopathy by seven-field photography and for secondary intervention had type 1 diabetes for 1–15 years and very mild tolevels should result in more appropriate and consistent referrals to treatment centers. Optical coherence tomography Optical coherence tomography provides images by projecting a pair of near infrared light beams into the eye. The resulting interference pattern from these beams is dependent of the thickness and reflectivity of the retinal structures and is detected by the measuring system . The images produced appear to be cross- sections of the retina and allow the thickness of the retina to be measured. The thickness of the retina may allow DME to be followed in a quantitative manner Patients were randomized to either conventional or intensive treatment. Conventional treatment was comprised of one to two daily injections of insulin, without daily adjustment in insulin dosage. The goals of the treatment were absence of symptoms from glycosuria and hyperglycemia, absence of ketonuria and frequent serious hypoglycemia, and normal growth and development of ideal body weight. Patients assigned to intensive treatment received more than three injections of insulin or insulin by an external pump with the goal of achieving normal glycemia. The main outcome measure was a three-step change in retinopathy level on fundus photography that was sustained for 6 months. Of the 1,441 patients in the DCCT, followed for a mean of 6.5 years, 99% completed the study and 95% of all scheduled examinations were completed.

ASPIRIN TREATMENT

The Early Treatment Diabetic Retinopathy Study (ETDRS) investigated whether aspirin (650 mg/day) could retard the progression of retinopathy. After examining progression of retinopathy, development of vitreous haemorrhage, or duration of vitreous haemorrhage, aspirin was shown to have no effect on retinopathy. With these findings, there are no ocular contraindications to the use of aspirin when required for cardiovascular disease or other medical indications.

LASER PHOTOCOAGULATION

The Diabetic Retinopathy Study (DRS) investigated whether scatter (pan retinal) photocoagulation, compared with indefinite deferral, could reduce the risk of vision loss from PDR. After only 2 years, photocoagulation was shown to significantly reduce severe visual loss (i.e., best acuity of 5/200 or worse). The benefit persisted through the entire duration of fol- low-up and was greatest among patients whose eyes had high-risk characteristics (HRCs; disc neovascularization or vitreous haemorrhage with any retinal neovascularization). The treatment effect was much smaller for eyes that did not have HRCs.

Anti-Inflammatory Therapy/Intravitreal Steroid

Intravitreal corticosteroids have become increasingly important in the treatment of DME, especially in refractory DME and cases lacking a response to anti-VEGF therapy . Refractory cases of DME and nonresponses to anti-VEGF are presumed to be driven by multiple cytokines. As potent anti-inflammatory agents, corticosteroids target a broad array of mediators involved in the pathogenesis of DME including VEGF, TNF-α, chemokines, leukostasis and phosphorylation of tight-junction proteins. Currently, intravitreal corticosteroids used in the clinical trials for DME treatment include the off-label triamcinolone acetonide, the FDA-approved dexamethasone (DEX) intravitreal implant and the fluocinolone acetonide (FA) intravitreal implant. In the DRCR Protocol I trial, intravitreal triamcinolone showed promising efficacy in improving visual acuity

Non-Steroid Anti-Inflammatory Drugs

As one of the most important proinflammatory cytokines present in the vitreous of DR patients, IL-6 has been investigated as a promising target for anti-inflammatory therapy for DR. Antibodies against IL-6 (EBI-031) and the IL-6 receptor (tocilizumab) have been developed. Clinical trials have been carried out to test the efficacy and safety of EBI-031 (clinicaltrials.gov ID: NCT02842541) and tocilizumab (clinicaltrials.gov ID: NCT02511067) in patients with DME

Laser Treatment/Traditional Laser Treatments

Laser photocoagulation has been the gold standard for the treatment of both DME and PDR before the advent of anti-VEGF therapy. Focal/grid macular laser therapy was shown to effectively alleviate edema of the macula and reduced the risk of moderate visual loss by 50% in the three-year Early Treatment Diabetes Retinopathy Study (ETDRS) . Panretinal photocoagulation (PRP) has also been used for the treatment of PDR and significantly reduced the risk of severe visual loss, especially in cases with high-risk complications such as vitreous hemorrhage . The exact mechanisms by which laser therapy reduces DME and induces regression of neovascularization remains unclear.

PREVENTIVE METHOD

Systemic Control and Preventive Intervention

As the prevalence of diabetes worldwide continuously increases, incidence of vision-threatening diabetic retinopathy is projected to nearly triple in the next 40 years. For patients diagnosed with diabetes, the most important method of preventing visual complications, such as retinopathy, is to control the diabetes at a systemic level. Tight regulation of glycemia via intensive insulin therapy significantly reduces the risk for retinopathy prevalence and progression. In addition to its effect on glycemic and circulating insulin levels, systemic insulin therapy has been shown to have a local impact on ocular tissue as well, including restoration of retinal insulin receptor signaling cascade and rod photoreceptor function. We recently demonstrated that both components of systemic insulin treatment—normalization of glycemia and insulin signaling, including locally—were critical in restoring normal retinal function. Hypertension is another well-known systemic effect of diabetes that can necessitate specific intervention. Indeed while there are conflicting reports on the benefit of antihypertensive therapies alone, combined control of glycemia and blood pressure has been clearly shown to significantly delay the onset and slow the progression of diabetic retinopathy.

Serum lipid levels have also gained recent attention for their potential impact on vision loss in patients with diabetes. Specifically, dyslipidemia and elevated low-density lipoprotein (LDL) have been shown to be significantly associated with retinal hard exudate formation. These factors, along with total cholesterol elevation, are also associated with the occurrence of DME. A correlation between triglyceride levels and diabetic eye disease has been suggested as well, though its impact on retinopathy specifically is debated. Further studies are investigating the preventive impact of lipid-lowering agents, such as fibrates and statins, and the first reports have showed a positive impact on reducing diabetic retinopathy onset and progression. However well achieved, careful regulation of glycemia, blood pressure, and lipid serum levels does not eliminate the potential for vision complications, demonstrating the existence of other risk factors. Different epidemiologic studies have shown that smoking males with type 1 diabetes have a higher prevalence of ocular disease. An association was also reported between ocular perturbations and previous diagnosis of albuminuria or diabetic nephropathy. Additional risk factors include puberty, pregnancy, and, most obviously, duration of disease. Therefore consistent screening is necessary for early detection. It is recommended for type 1 patients with diabetes to receive a comprehensive ophthalmic examination 3 to 5 years after diagnosis, while type 2 diabetics should begin being monitored immediately after diagnosis. Women trying to conceive should have an additional exam prior to conception and during the first trimester.30 Continued dilated eye examinations are recommended annually for asymptomatic patients, with suggested follow-up frequency increasing with diabetes duration and symptom severity

1.Get a Yearly Eye Exam

Diabetes can cause retinopathy, or damaged blood vessels in the backs of your eyes. You may have no symptoms at first. If it worsens, you can lose your eyesight. Once a year, get a dilated eye exam from an ophthalmologist or optometrist. They'll check for early signs of retinopathy in case you need to treat it to save your vision.

2.Control Your Blood Sugar

You're more likely to get diabetic retinopathy if your blood sugar isn't well-controlled. Check your blood sugar levels several times a day or use a continuous glucose monitor. If you're under stress or sick, you may need to check it more often. Try to keep your blood sugar levels in healthy target ranges. Generally speaking, this is 80-130 milligrams per decilitre (mg/dL) before meals and less than 180 mg/dL 1-2 hours after meals

3. Keep an Eye on Your A1c

Your doctor can give you a haemoglobin A1c test to measure your average blood sugar levels over the previous 3 months. Your goal should be an A1c score under 7%, but it may be higher if you're older or have other health conditions. Talk with your doctor to set your personal A1c goal.

4. Watch Your Other Numbers Too

High blood pressure and cholesterol also raise your chances of diabetic retinopathy. Your doctor can test your blood pressure and cholesterol. If your numbers are high, they'll suggest changes to your diet, weight loss, or more exercise. If that doesn't help, they can prescribe medications for you.

5. Cut Back on Salt

High levels of salt or sodium in your diet can cause high blood pressure. You may not have any symptoms that tell you there's a problem. Try using herbs and spices for flavour instead of salt. Low-salt diets also help reduce inflammation in the tiny blood vessels in your eyes and keep them healthy

6. Less Fat, More Fruit

Eat a balanced diet lower in fat and sugar, as well as sodium. Try the Mediterranean diet, or eat lots of fresh fruit, veggies, and fish, to help prevent retinopathy. Obesity also raises your risk of this eye disease. The Mediterranean diet can help you manage your weight, too.

7. Stop Smoking

If you smoke tobacco, it's time to kick the habit. Smoking raises your risk of diabetic retinopathy. Ask your doctor for help in quitting. You may need counselling and prescription medicine to help you fight the urge to smoke.

8. Get Plenty of Exercise

Regular exercise keeps your eyes healthy and helps you control your diabetes, because it helps lower blood sugar. Shoot for 150 minutes of moderate-intensity exercise each week. Like to walk? Strap on a pedometer. Aim to walk 10,000 steps every day. Find exercises that are fun, so you stay motivated to do them.

9. Tame Your Stress

High stress increases your risk of diabetes complications like retinopathy. It boosts hormones like cortisol and adrenaline that cause insulin resistance, which can raise your blood sugar. Find ways to control stress, like getting enough exercise and sleep.

10. Limit Your Alcohol

If you drink, do it only in moderation. Stick to one serving per day for women, two per day for men. Alcohol may interfere with diabetes meds or cause serious blood sugar dips. Some new research shows that moderate wine drinking could even help protect you from diabetic retinopathy, but don't overdo it.

11. Watch for Vision Changes

If you notice sudden vision changes like spots, haze, blurring, eye pain or redness, floaters, or loss of eyesight, contact your eye doctor right away. Don't wait until your yearly eye exam to bring up these symptoms. You may need treatment to slow down or prevent vision loss.

PREVENTION

Risk factors associated with diabetic retinopathy development and progression include hyperglycemia, dyslipidemia, and high blood pressure. Strict glycemic control has been established as absolutely key in preventing diabetic retinopathy progression, but evidence is mixed for targeting dyslipidemia and high blood pressure as measures specifically to prevent or slow the progression of diabetic retinopathy.

Hyperglycemia

Strict control of hyperglycemia is essential in minimizing the risk of diabetic retinopathy development or progression.The Diabetes Control and Complications Trial reported a strong relationship between risk of diabetic retinopathy and mean HbA1c: a decrease of about 10% in HbA1c resulted in a 39% decrease in risk of diabetic retinopathy progression.8 Long-term follow-up also showed that strict blood glucose control decreased the incidence of progression in severe NPDR, proliferative diabetic retinopathy, and clinically significant macular edema.

Dyslipidemia

Elevated serum cholesterol and triglyceride levels have been implicated as risk factors for diabetic retinopathy. However, studies of the effect of statin and fibrate treatment specifically on diabetic retinopathy development and progression have produced mixed results.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial30 investigated intensive glycemic control and treatment of dyslipidemia in patients with type 2 diabetes (median baseline values for the dyslipidemia group were high-density lipoprotein cholesterol of 38 mg/dL, low-density lipoprotein cholesterol 93 mg/dL, and triglycerides 162 mg/dL). After 4 years of follow-up, the study reported reduced rates of diabetic retinopathy progression with intensive glycemic control combined with fenofibrate and simvastatin treatment vs simvastatin plus placebo. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study reported a decreased need for laser treatment in patients with diabetic retinopathy treated with fenofibrate. Other studies reported that statin therapy decreased the risk and incidence of diabetic retinopathy, while others found that statins do not protect against diabetic retinopathy progression.

Blood pressure

The role of blood pressure management in the prevention of diabetic retinopathy has been explored. A Cochrane review showed that although intensive blood pressure control was associated with a reduced risk of diabetic retinopathy development, it did not significantly impact progression of existing diabetic retinopathy compared with less stringent measures of blood pressure control.

CHALLENGES IN DIABETIC RETINOPATHY

-Barriers to early detection and treatment

-Accessibility issues in low resources setting

-Patient adherence to treatment protocols

-Current gaps in research and clinical care

-Psychosocial aspects of DR management

-Impact on mental health and quality of life

-Patient education and awareness

FUTURE DIRECTIONS:

PKC inhibitors Two PKC inhibitors are being developed to reduce microvascular complications in patients with diabetes. One of these, Ruboxistaurin (LY333531), is a specific inhibitor of PKC-(109) and has been found to block vascular complications of diabetes, including abnormalities in retinal blood flow, neovascularization, and VEGF-mediated effects on permeability in animal models In a small trial (n 29) of diabetic patients with no or minimal retinopathy, the drug was well tolerated with no adverse events noted and normalized mean circulation time and retinal blood flow abnormalities. The PKC- Inhibitor Diabetic Macular Edema Study (PKC-DMES) was a multicentre, multinational, double- masked, placebo-controlled trial with patients followed for up to 52 months. The trial included 686 patients with DME and mild-to-moderate NPDR. There was no statistically significant reduction in pro- gression of retinopathy or incidence of macular edema found in this trial. How- ever, Ruboxistaurin, when given at 32 mg, displayed a trend (P 0.041) toward a positive

effect on the secondary outcome of occurrence of DME involving or imminently threatening the center of the macula. When patients with poor glycemic control at baseline were excluded (defined as HbA1c 10%), Ruboxistaurin displayed a borderline positive effect (P 0.019) on the occurrence of DME involving or imminently threatening the center of the macula. Additional clinical trials are under way to assess whether LY333531 can delay or stop the progression of diabetic retinopathy and macular edema at their earliest stages. The second PKC inhibitor, PKC412,is under development for treatment of diabetic retinopathy .

CONCLUSION:

Individuals' risk of developing diabetic retinopathy is currently increasing at a rapid pace. Nonetheless, studies are still being conducted to understand the underlying pathophysiology. In order to stop the progression of retinopathy, this review addresses a number of mechanisms and potential treatment targets. Current treatments for DR, including as blood pressure control, glycaemic control, anti-inflammatory corticosteroid use, and focused laser treatment, have been shown to be effective in previous studies, despite several drawbacks. However, other pharmaceuticals have also showed promise, including AGE inhibitors, antioxidants, and antiplatelet drugs. To get around the problems and create therapies that work with fewer side effects, further research is needed.

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