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Review Article

A Review on Diabetic Retinopathy: Classification, Risk Factors & Treatment

Manisha[1], Amandeep Kaur[2], Harinderjit Singh[3], Hanumanthrao Patil[4], Rajesh Kumari Patil[5]

[1,2]Pharm.D Scholar, Adesh Institute of Pharmacy and Biomedical Sciences, Adesh University, Bathinda

[3]Associate Professor, Department Pharmacognosy, Adesh Institute of Pharmacy& Biomedical Sciences, AU, Bathinda

[4]Professor & Principal, Department of Pharmacy Practice, Adesh Institute of Pharmacy & Biomedical Sciences, AU, Bathinda

[5]Professor & HOD, Department of Pharmacy Practice, Adesh Institute of Pharmacy & Biomedical Sciences, AU, Bathinda

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Corresponding author: Rajesh Kumari Patil

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Abstract:

The main factor contributing to visual loss in middle-aged adults is diabetic retinopathy. The management of this disease depends on maintaining blood pressure, blood lipids, and blood glucose. We examine the risk factors for the development of high-risk proliferative diabetic retinopathy (PDR), as well as other risk factors of DR such as hyperglycemia, obesity, hypertension, hyperlipidemia, puberty and pregnancy, and myopia, in order to ascertain the relationship between the severity or stage of diabetic retinopathy and associated risk factors. Early detection and prompt treatment allow prevention of diabetes-related visual impairment and to lessen the impact of DR-related visual loss. The use of laser therapy has been modified and for the development of severe visual loss or vitrectomy in eyes assigned to deferral of photocoagulation in this study, non-proliferative diabetic retinopathy is graded as mild, moderate, or severe based on the presence of hard exudates.

Keywords: Diabetic retinopathy, risk factors, non-proliferative diabetic retinopathy, diabetic macular edema, anti-VGEF.

Introduction

The eye disorder known as diabetic retinopathy, which is brought on by high blood sugar levels that harm the eyes, can result in vision loss and even blindness in those who have diabetes. Patient will experience symptoms including blurry vision, seeing color look faded or washed out, and having poor night vision as diabetic retinopathy worsens. Symptoms of diabetic retinopathy typically affect both eyes. Thus, new blood vessels begin to form in the eye. Patients with DM are more likely to experience retinal abnormalities, ocular impairment, and blindness all of which can result in DR complications affecting the eyes. The most significant factor contributing to vision loss and blindness in diabetics is a micro-vascular complication of diabetes mellitus (DM), which affects the tiny blood vessels that link the veins and arteries in the eyes. It develops consequent to an increase in blood sugar levels. Around the world, working-age persons with diabetic retinopathy continue to have severe acquired vision loss. This disease has significant medical, societal, and economic effects. If fundus screening and early treatments are carried out on people with diabetes, DR, a condition that has become a serious concern to public health, can be averted and the risk of blindness can be decreased. Diabetes mellitus, the most prevalent endocrine disorder in the world, is characterized by chronic hyperglycemia, which in turn results in a number of micro-vasculopathy and neuropathic abnormalities that compromise various organs and cause diabetic retinopathy (DR), diabetic nephropathy, renal failure, autonomic neuropathy, and cardiovascular complications. Increased awareness of DR among diabetic patients would allow them to adopt a different mindset towards routine doctor visits and early eye exams. By managing diabetes and associated ocular co-morbidities better, this will assist to reduce the risk of vision loss caused by DR. Microaneurysms, or localized dilations of retinal micro-vessels, which are most frequently observed as deep red spots in the posterior part, are the early clinical lesions of diabetic retinopathy. Typically, these lesions develop over time and vanish without causing any symptoms. The hard exudates seen on fundoscopy are caused by a break-

down in the blood-retinal barrier as well as the release of many inflammatory cytokines and plasma proteins. Severe hypoxia causes neovascularization, vitreous haemorrhage and retinal detachment at the ultimate stage of diabetic retinopathy. Severe NPDR, PDR, or clinically significant macular edema were all considered to be signs of sight-threatening retinopathy. According to earlier research, 25% of all diabetes patients smoke. Diabetes that is uncontrolled and is allowed to progress can harm the microvasculature of the body's most important organs, including the kidneys and eyes. When the micro aneurysms rupture, haemorrhages happen. Bright-yellow colour lesions, such as hard exudates are caused by fluid leaking into the retinal surface from capillaries or from micro aneurysms occlusions of the nerve fibre layer cause soft exudates, sometimes known as cotton wool patches, which are other bright white lesions. It can also increase your risk of developing other eye diseases. Measurement of the pressure inside the eye, evaluation of the ocular structure, including evaluation of the retina through a dilated pupil, and patient history to determine vision difficulties, presence of diabetes, and other general health concerns that may be affecting vision are some of the procedures that may be used when evaluating the retina and macula.

Classification of Diabetic Retinopathy

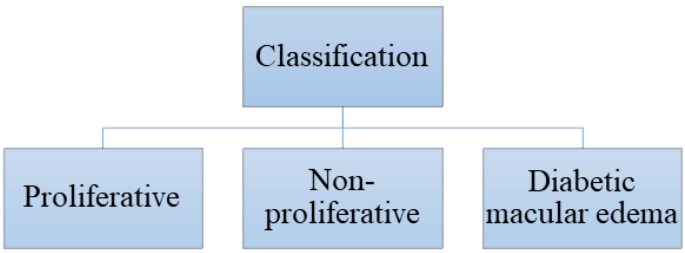

Figure 1:

There are Two Types of Diabetic Retinopathy are

- Proliferative (advanced form of disease)
- Non-proliferative (early stages of diseases)

Proliferative Diabetic Retinopathy

The more severe stage of diabetic eye disease is called PDR. The clear, jelly-like material (vitreous), which fills the centre of your eye, might seep into these nascent blood vessels because they are weak.The retina may eventually separate from the back of your eye as a result of scar tissue produced by the development of new blood vessels. The eyeball may become pressurized if the additional blood vessels obstruct the usual drainage of fluid from the eye. Neovascularization of the retina is the term used most frequently to describe the development of new vessels.

Non-Proliferative Diabetic Retinopathy

Vascular walls of the retina deteriorate. Small bulges that occasionally leak fluid and blood into the retina protrude from the walls of the smaller veins. Larger retinal vessels may start to enlarge and develop uneven diameters. Blood vessels are clogged, NPDR can worsen from mild to severe. It is necessary to stop irreversible vision loss if macular edema impairs vision.

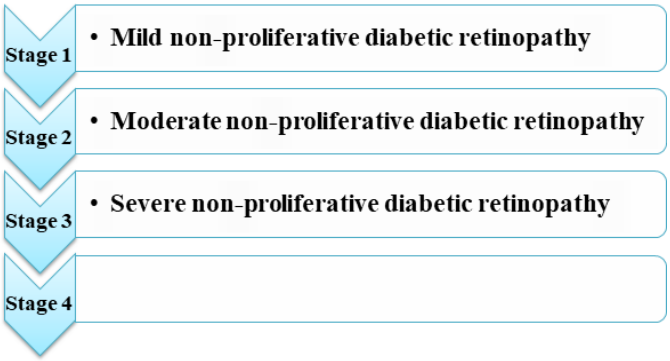

Figure 2:

Stage 1: Mild non-proliferative diabetic retinopathy

This is the first stage of diabetic retinopathy, which is characterized by minute swellings or bulges in the retina's blood vessels. The macula, the rear of

the retina, may expand as a result of these microaneurysms' potential to let minute amounts of fluid into the eye. Exudates and at least one microaneurysm may be seen in the Mild NPDR stage. In mild NPDR, microaneurysms frequently develop in the centre of the hard exudate ring.

Stage 2: Moderate non-proliferative diabetic retinopathy

The microscopic blood vessels at this stage continue to expand, obstructing blood flow to the retina and inhibiting proper nutrient delivery. Only when blood and other fluids accumulate in the macula and create impaired vision. The moderate NPDR is made up of many haemorrhages and microaneurysms together with exudates. Haemorrhages may also occur because of the weakness of small capillarity that is placed close to microaneurysms when microaneurysms are detected as dark/red little spots in the retina, a condition known as moderate non-proliferative diabetic retinopathy (NPDR).

Stage 3: Severe non-proliferative diabetic retinopathy

The retina blood flow is significantly reduced at this stage because a bigger portion of the retina blood vessels obstruct, contributing to the condition. These new blood vessels, which are incredibly fragile and delicate, result in retinal edema, which causes eyesight blurriness, dark spots, and even patches of vision loss. Sudden and permanent vision loss could result if these veins spill into the macula. When NPDR is severe, the presence of haemorrhages, soft exudates, microvascular changes, and a significant lack of oxygen can cause proliferative diabetic retinopathy, which leads to neovascularization.

Stage 4: Proliferative diabetic retinopathy

Due to their fragility, newly formed blood vessels bleed and leak more frequently. Additionally, the related scar tissue may constrict and result in retinal detachment, which would impair vision indefinitely. In the eye, scar tissue develops as a result of these blood vessels, which are delicate and prone to bleeding.

Diabetic Macular Edema

It is a complication that has been evaluated separately from the DR phases. Any level of diabetic retinopathy can cause DME in an eye. In the macular region, DME manifests as focal or widespread retinal thickness. One of the main diabetes consequences, diabetic macular edema (DME), is also the biggest contributor to partial and complete blindness. DME impairs central vision, causing blurred vision and distortion of a portion of the visual field that can make it difficult to perform tasks like reading, driving, or walking. As a result, a precise diagnosis is essential for the right course of therapy to be taken in order to prevent health risks and the related costs. DME are classified as:

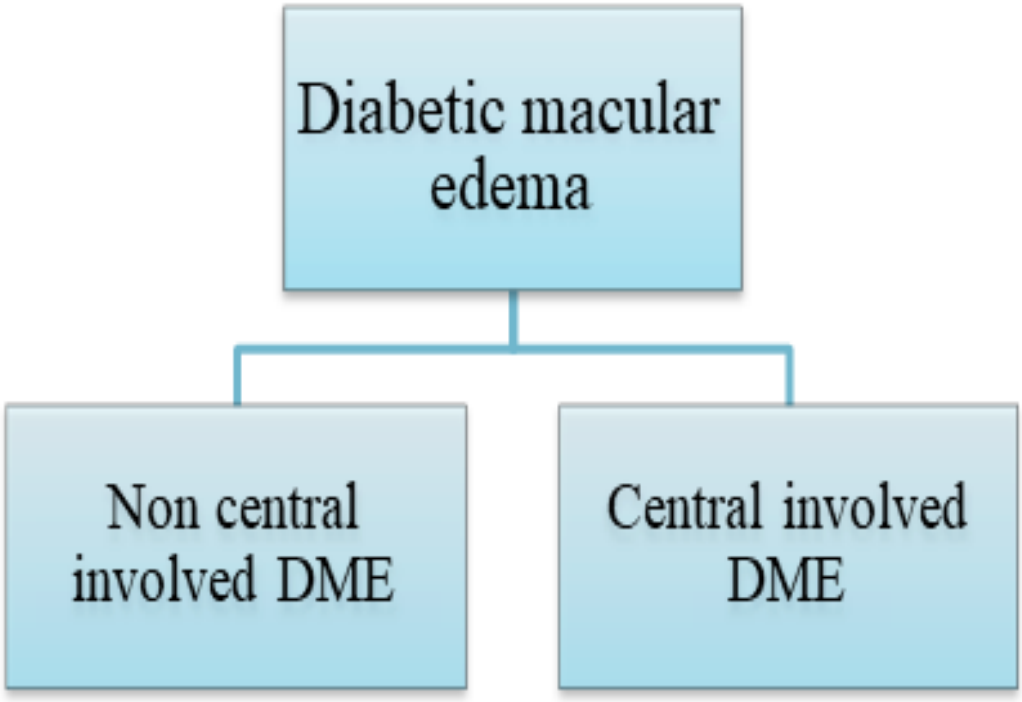

Figure 3:

Risk Factors

Figure 4:

Modified Risk Factor

Hyperglycemia

A frequently used marker for assessing glycemic management is glycated haemoglobin. Microvascular problems are considerably decreased by good glycemic management. The haemoglobin (HbA1c) value, which represents the blood sugar level over the previous three months, is analysed to assess glycemic management. Instead of slowing or stopping the advancement of DR, strict glycemic management is more effective. Consequently, the target HbA1c level should be established in accordance with the patient in order to minimize the onset and progression of DR and to lessen consequences related to hypoglycemia.

Hypertension

It has repeatedly been shown that the onset of diabetic retinopathy is positively correlated with hypertension. Cotton wool patches, hard exudates, and micro-aneurysms were statistically considerably less likely to form when blood pressure was tightly controlled with level of 150/85 mmHg or below. Despite having perfect blood pressure control, the trial revealed that both groups had poor glycemic control, which may have contributed to the advancement of diabetic retinopathy. When it comes to the advancement of DR, there is no observable difference between the group that received normal treatment (systolic BP > 140mmHg) and the group that received rigorous blood pressure management (systolic BP >120mmHg).

Obesity

Obesity is a part of metabolic syndrome, or another risk factor frequently linked to cardiovascular disease. It can be identified by the waist-hip ratio, waist circumference, and body mass index (BMI). The researchers found that the underweight patients had diabetes for a longer time and were also more likely to be taking insulin than the obese subjects. Therefore, postulated that the underweight patients may have poor overall glycemic control and were therefore in a more "severe" phase of diabetes as compared to their obese patient.

Hyperlipidemia

Patients with varying degrees of diabetic retinopathy have identical cholesterol levels, with no statistically significant differences. Hard exudates that are characteristic of NPDR are more common when serum lipid levels are raised. A positive association between the triglyceride level and the severity of

DR was found, while a negative correlation was found between the triglyceride level and HDL level. DR and total cholesterol levels were not observed to be correlated in the study. According to the findings of a meta-analysis, diabetic individuals with DMO had higher levels of triglycerides, LDL cholesterol, and total cholesterol. Hard exudates in the retina increase when fat and cholesterol levels are high.

Non-Modified Risk Factor

Duration of Diabetes

The most significant non-modifiable risk factor for DM is disease duration, and as the disease duration grows, so do the frequency and severity of DR and DMO. According to earlier research, patients with DR experience longer disease durations than patients without DR. After 10 years, DR incidence was found to be 74%, DMO to be 20–25%, and after 25 years, these rates were 97% and 29%, respectively. Microvascular damage rises as diabetes progresses and as people are exposed to hyperglycemia for longer periods of time.

Puberty & Pregnancy

After puberty, the probability of acquiring DR was seen to rise by 30%. This impact is transient during pregnancy and quickly resolves after delivery, it did emerge in 12.5% of the pregnant patients with DM prior to delivery, of whom 6.3% required laser treatment. Particularly in T1DM, DR can deteriorate quickly throughout puberty and pregnancy, with a 30% increased risk of developing DR when comparing the time before and after menarche. Women who have PDR during pregnancy may benefit from early pan-retinal photocoagulation treatment and diligent monitoring during the pregnancy and afterwards.

Chronic Kidney Diseases

The micro-vascular consequences of diabetic retinopathy include retinopathy and nephropathy. A glomerular filtration rate (GFR) estimate for chronic renal disease is 60 ml/min. In patients with or without diabetic retinopathy, microalbuminuria and a greater albumin-to-creatinine ratio were also linked to diabetic retinopathy. It has been proposed that in diabetic patients, chronic hyperglycemia results in micro-vascular alterations in both the retina and glomerulus of the kidney. These micro-vascular alterations cause the capillary lumina to constrict and occlude, causing inadequate perfusion to the tissues and retinopathy and nephropathy.

Myopia

Myopia is hazardous to eye health; it has been noted that myopic patients have a lower incidence of diabetic retinopathy. Axial length, the primary contributor to myopia, was discovered to also be linked to diabetic retinopathy, with each millimetre increase in axial length being linked to a lower risk of developing diabetic retinopathy.

Genetic Factor

Due to genetic variations, some people with long-term uncontrolled diabetes experience mild DR, whereas others with severe DR develop in those who have risk factors under sufficient control. Studies on families and twins have indicated that people with a family history of DR have a higher probability of having the condition than people without one.

Treatment

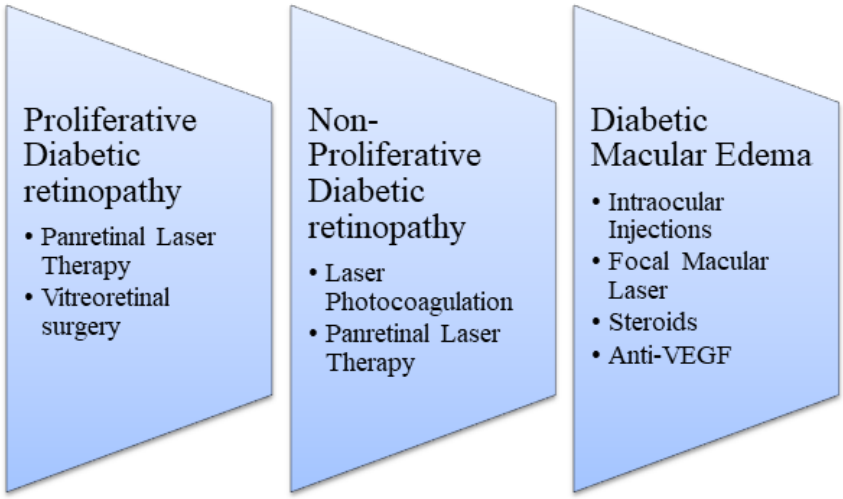

Figure 5:

Vitrectomy

Vitreoretinal surgery is a costly and complex procedure that should only be performed by vitreoretinal specialists skilled in this technique. It is typically saved for PDR complications that will ultimately result in blindness, such as severe vitreous haemor-

rhage and secondary retinal detachment. These have increased the number of cases when vitrectomy is indicated and may enhance results. A vitrectomy may help diffuse or widespread DME that is resistant to targeted laser therapy. When a vitreous haemorrhage occurs early in an insulin-dependent diabetic, or after six months in a non-insulin-dependent diabetic, and it does not heal, a vitrectomy is indicated. During this treatment, scar tissue that is pulling on the retina, as well as blood from the vitreous (the middle of the eye), are removed. The procedure can be utilized to treat macular edema even though these issues are uncommon in early stages of retinopathy. It is also performed when extensive scar tissue has developed.

Anti-VEGF

Regarding the pathogenesis of retinal neovascularization and BRB modification, VGEF has been the most significant factor. Fluid eruption and retinal edema are the results of how it impacts endothelial tight junction proteins. Pegaptanib, an anti-VEGF aptamer, ranibizumab, a monoclonal antibody fragment, and bevacizumab, a full-length antibody are medications that directly inhibit the VEGF molecule. Other therapies include soluble VEGF receptor analogues, VEGF-Trap, and bevasiranib small interfering RNAs. Under topical anaesthetic, intravitreal injections of anti-VEGF medications are administered into the eye. A monoclonal antibody called ranibizumab, which has been "affinity-enhanced" for greater binding affinity to VEGF-A, inhibits all isoforms of VEGF-A. Ranibizumab is roughly three times as big as bevacizumab, which likewise blocks all VEGF-Aisoforms. When treating PDR patients with considerable fibrovascular proliferation, anti-VEGF medications must be used with caution because they could worsen retinal detachment.

Pan-Retinal Laser Photocoagulation

The treatment of choice for severe non-proliferative and proliferative DR is pan-retinal laser photocoagulation (PRP), which involves laser burns being applied to the entire retina while sparing the central macula. To reduce the oxygen demand of the hypoxic retina in diabetic retinopathy, photocoagulation is used to graded burn the posterior 45°–60° of the retina, away from the vascular arcades of the macula. This process turns the hypoxic zones of the retina into anoxic zones, which inhibits the release of vaso-proliferative factors. Burns cause the aberrant new blood vessels to contract and scar.

Steroids

The reduction of inflammation is its primary mechanism of action. By strengthening the blood-retina barrier's adhesion molecules, they help lessen vascular permeability. Steroids not only reduce inflammation but also block VEGF. The anti-inflammatory and anti-angiogenesis effects of corticosteroids are strong. The DRCR Protocol has demonstrated that intravitreal steroids are effective in treating diabetic macular edema. In some diabetic macular edema patients who struggle to control their condition with anti-VEGF medications alone, combining anti-VEGF medications and steroids may be more beneficial.

Laser Photocoagulation

The treatment of diabetic retinopathy has undergone a significant transformation with the development of laser photocoagulation of the retina. Macular photocoagulation is the process of using light to destroy non-proliferative diabetic retinopathy that has clinically significant macular edema. To avoid grid macular photocoagulation leakage, diffuse leakage around the macula may be treated with photocoagulation. Using fundus fluorescein angiography (FFA), diffuse or focal leakage can be detected. A contrast agent called sodium fluorescein is injected into the blood during FFA to take a black-and-white retinal image. This laser procedure, sometimes referred to as a focused laser treatment, has the ability to stop or reduce ocular fluid and blood leaks. The purpose of laser therapy is to reduce endothelial and retinal pigment epithelial dysfunction and remove macula leakage. Focused laser is used to treat aneurysm-related leaks, and grid laser is used to treat leaks developing in the capillary bed.

Conclusion

Patients with severe DR and macular edema have a lower risk of losing their vision after receiving panretinal and focal retinal laser photocoagulation. With prompt detection and the right interventional therapy, diabetic retinopathy-related blindness can now be mostly avoided. The fundamental ophthalmic care of the diabetic patient requires routine, recurrent, lifelong, expert clinical retinal examination. For the time being, the important factor in stopping or preventing diabetic retinopathy is maintaining strict management of blood glucose levels and hypertension.

Intravitreal administration of anti-VEGF medicines is still widely employed by ophthalmologists in advanced stages of diabetic retinopathy despite evidence supporting its efficacy and safety. The issue of the systemic inhibition of angiogenesis is potentially solved by intravitreal injection, which enables antiangiogenic medications to successfully reach the retina. Anti-VEGF medications have the potential to enter the systemic circulation and cause systemic problems as well. Visual impairment caused by diabetes can be avoided with early detection and appropriate treatment. To stop the onset and progression of DR and other diabetes-related complications, patients with diabetes need to have

regular follow-up visits with primary care doctors to ensure that their glycemic, blood pressure, and lipid control are optimized.

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