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A Review of Diabetic Retinopathy-Pathophysiology, Clinical Presentation, and Management

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Introduction: Diabetes is a metabolic disease that can lead to DR. So DR is nothing but a complication of diabetes mellitus which is characterized by gradual progressive loss of vision, macular oedema, blurred vision, floaters, etc. It is crucial to understand the severity of the disease and the risk factors associated with the disease to prevent the disease and reduce the incidence and prevalence of the disease. Also, there is a need for the screening of the disease to facilitate early detection of the disease and prevent the population from blindness. The aim of the review is to understand the disease according to its clinical features, grading and to learn more about the development in medicine for the management of the disease.
Methodology: Various literature search was performed up to November 2021 to understand the disease and its presentation in different stages. Various sources used are Pubmed, Mayo clinic, Google scholar. And then all research articles were thoroughly analyzed and combined to understand the pathophysiology, clinical presentation, and management of DR in different stages.
Result: DR is a microvascular disease and a complication of diabetes mellitus. There are various risk factors, hypothesis for the pathophysiology of the disease. All the information was summarized and presented in this review article
Conclusion: DR is a manageable disease and the best way to manage DR is by controlling blood sugar level, changing lifestyle and preventing the modifiable risk factors to prevent the progression of the disease.

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Keywords: Diabetic retinopathy; DR; pathophysiology; risk factors; diagnosis; clinical presentations; management.

1. INTRODUCTION

Diabetic Retinopathy (DR), can also be called diabetic eye disease (DED) [1], is a disorder wherein retina is damaged as a result of diabetes mellitus. In developed nations, it is the major cause of blindness [2]. Diabetes is expected to rise rapidly in the upcoming times [3,4]. Type 2 diabetes (T2D) has already reached epidemic proportions, whereas type 1 diabetes (T1D) is becoming more common. Damage to the blood vessels of the light-sensitive tissue at the rear of the eye (retina) causes Diabetic Retinopathy [5]. Anyone with type 1 or type 2 diabetes can acquire the illness [5]. The longer you have diabetes and the less well your blood sugar is regulated, the more probable it is that you may get this eye issue [5]. Clinical signs of vascular anomalies in the retina are used to make the diagnosis of DR [6]. DR is classified into two types: non-proliferative DR (NPDR) and proliferative DR (PDR) (PDR). NPDR is the first stage of DR, characterized by increased vascular permeability and capillary occlusions in the retinal vasculature. The severe stage, proliferative DR, is distinguished by the formation of new vessels. Diabetic macular oedema is the most common cause of vision loss in diabetic people (DME). DME is defined by swelling or thickening of the macula as a result of sub and intra retinal fluid build-up in the macula caused by a interruption of the blood-retinal barrier [7]. DME can cause visual image alteration [6]. Current DR therapies, including as intravitreal pharmacologic medicines, laser photocoagulation, and vitreous surgery, are intended at managing microvascular complications. Intravitreal anti-VEGF medications are being used to treat early as well as severe cases of DR. While standard laser surgery provides stability in vision, anti-VEGF therapy can result in better vision with fewer side effects. Many therapy techniques have been adopted to control DR, and it is hoped that better treatments will be recorded and employed in the near future.

2. PATHOPHYSIOLOGY

Hyperglycaemia and Retinal Microvasculopathy: DR is a disease that affects microvessels. High blood sugar acts as a significant risk factor for the damage of microvessels in retina. There are many metabolic pathways for high blood sugar inducing damage in microvessels [8].

Vascular dilation and alterations in blood are the primary reactions of the vasculature in the retina to hyperglycaemia. These changes represent metabolic autoregulation to boost diabetic retinal metabolism [9]. Loss of pericyte is also a symptom. Self-programmed death in pericytes mediated by excessive hyperglycemia has been demonstrated in both in vitro and in vivo experiments [10,11]. Cell death of endothelial cells and thickened basement membrane contribute to the blood-retina barrier [12]. Many angiogenic factors help in the regulation of vascular permeability.

Inflammation: Inflammation plays a very important role in the pathogenesis of DR. In different stages of DR, there are cases of chronic loss-grade inflammation. Leukostasis is found in the early stages of DR. Studies have shown leukocytes get adhered in the vessels of retina after just 3 days of induction of Diabetics [6]. Leukostasis is also related with damage of endothelial cells and BRB damage as Leukostasis leads to loss of endothelium and BRB failure [6].

Malfunctioning of the glial cell in retina is also thought to have a role in the beginning and progression of retinal inflammation in DR [6].

Nerve degeneration of retina is found in early stages of DR [6]. Apoptosis of neurons starts 1 month after induction of diabetes. Mitochondrial dysfunction is also responsible for retinal degeneration in DR. Research studies have shown that hyperglycemia leads to fragmentation of the cellular mitochondria and programmed death of cell.

2.1 Risk Factors

Hypertension: In 10 years, it has been seen that a patient who increased blood pressure has more than twice the risk of developing DR than a normal diabetic patient. Changes in the morphology of retinal vessels similar to NPDR are seen in hypertensive patients.

Obesity: Obesity increases the prevalence of DR. Obesity with a BMI of >30 kg/m2 is a substantial predominant risk factor for diabetic retinopathy [13].

Sex: Male sex is also an independent risk factor for DR [13]. Some studies have shown that DR is more prevalent in males and males have a 50% higher risk of developing DR when compared to females. But new researches have failed to establish this theory.

Hyperlipidemia: There are reports of relation between total serum cholesterol and DR. DR is more prevalent in patients with elevated total serum cholesterol along with diabetic macular oedema.

Chronic kidney disease: Retinopathy and nephropathy includes some of the microvascular complications [13]. DR is associated with microalbuminuria. Studies have shown that chronic hyperglycemia causes changes in microvasculature in glomerulus of kidney and retina of eye which leads to narrowing and occlusion of vascular lumen leading to nephropathy and retinopathy.

Smoking is also associated with early progression of DR. But UKPDS50 study have shown protective effect of smoking on DR. Studies have shown the NPDR is more prevalent in smokers as compared to non-smokers.

Myopia: It is observed that the prevalence of DR is less among myopic patients. Myopia has negative association with DR. But some new researches are contradicting this fact but until now there are no proofs.

Table 1. Risk factors and its associate Modifiability

Risk factors	Modifiability	Association
Hypertension	Modifiable	Positive
Obesity	Modifiable	Positive
Sex	Unmodifiable	Indeterminate
Hyperlipidaemia	Modifiable	Indeterminate
Chronic kidney disease	Unmodifiable	Positive
Smoking	Modifiable	Indeterminate
Myopia	Unmodifiable	Negative

2.2 Grading

A National Screening Programme of UK has been implemented to meet targets [14]. This committee has produced grading criteria by the lesion detected during screening [14].

Level R0 – None
Level R1 – Background
Level R2 – Pre-proliferative
Level R3 – Proliferative
Maculopathy (M0 – nil present, M1 – maculopathy)
Unclassifiable (U)

2.3 Signs and Symptoms

In the early stages, there are no noticeable symptoms of DR but becomes apparent when the disease advances. The symptoms are usually bilateral as it affects both the eyes together.

The most common symptoms of DR are-

- The blurring of visual field
- Colour vision is impaired
- Floaters (spots that are present in the patient's visual field and have a peculiar property of moving in the direction of the patient's gaze)
- Patches in the visual field
- Poor night vision
- The central visual field is covered with dark spots
- Acute or complete loss of vision

2.4 Complications

DR is dreaded for its many complications.

Vitreous hemorrhage occurs when blood vessels bleed into the primary jelly that fills the eye, the vitreous.

Floaters are common in moderate instances, but vision loss is more common in severe cases.

Vitreous bleed can resolve spontaneously if the retina is not injured.

DR can sometimes result in a detached retina. If a detached retina is not treated, a person faces a substantial danger of losing their eyesight completely.

Glaucoma develops when flow of fluid becomes obstructed when new blood vessels grow [15]. The obstruction increases the chance of optic nerve getting injured and loss of vision by causing a build-up of pressure in the eye.

Floating specks in the patient's visual field, and significant loss of vision are common symptoms.

2.5 Diagnosis

DR can be diagnosed during an eye examination. There are various tests which are performed to diagnose DR which are as follows:

- Visual acuity test: Patient is asked to sit with an eye closed and asked to read Snellen's chart from various distances and eyesight is measured accordingly.
- Pupil dilation: Eye is dilated medically with the help of drugs which allows the ophthalmologist to see retina better which helps in finding the signs of DR.
- Ophthalmoscopy, also called as fundus photography, a type of retinal examination that uses a slit lamp biomicroscope and an exceptional magnifying lens to offer a close-up picture of the retina [2]. It can also be done using an indirect ophthalmoscope to obtain a broad view of the retina [3]. Fundus photography allows for the visualization of a vast area of fundus while also providing photo documentation for future reference.
- Fundus fluorescein angiography (FFA): This test uses fluorescein dye to detect any type of leakage or hypo-perfusion of the retina.
- Retinal vessel analysis: It identifies defects in the autoregulation of small retinal vessels in diabetics even before DR reveals itself [16]. This form of retinal response impairment is thought to be an early sign of vascular malfunction in diabetes, possibly foreshadowing a later risk of stroke [17].
- Optical coherence tomography (OCT): Laser beam interference is used in this test. It determines the thickness of the retina by generating a cross-sectional picture of the retina. As a result, any thickening in the retina may be observed [18].

Early signs of disease present in retina are:

- Leakage in vasculature
- Swelling between retinal layers (macular oedema)
- Fatty exudative deposits in between retinal layers
- Nerve injury
- Any other significant vascular changes

OCT and FFA are performed if macular oedema is suspected.

According to a recent study, certain parameters can help in detection of DR. they are:

1. diameter of vessel
2. velocity at which red blood cell flows
3. shearing stress on the vessel wall [18,19].

The conjunctival microvessels patterning has been proven to be effective for quick checking and diagnosis of DR at various stages [18,19].

UK has launched a program for the screening of DR every year for the whole population to prevent the disease from progression and decrease the incidence of disease.

3. MANAGEMENT

There are 3 major management techniques for DR, which have been proven quite effective in decreasing vision loss from this disease [20]. Even the patients who have advanced retinopathy also have 95% chance of prevention from vision loss if DR is treated before retina is severely damaged.

The treatment options available for the treatment of DR are as follows: -

- Surgery via laser photocoagulation
- Steroid injections and anti vascular-endothelial growth factor agents
- Surgical intervention in the vitreous

The above mentioned options are just for the managing of DR as it can't cure the disease. Along with these options there are some important therapeutic measures to manage the symptoms of DR like avoiding tobacco and correcting hypertension.

Obstructive sleep apnoea (OSA) is also associated with DR and its treatment will help in the management of DR.

The best way to prevent the disease from its progression is by controlling the blood sugar level and by achieving optimal glycemic control.

The above mentioned treatment options are very dangerous and they need to performed carefully as laser surgery can cause loss of retinal tissue.

Laser Photocoagulation It can be used to treat macular oedema as well as the whole retina to control neovascularization.

- Modified grid laser: A small region surrounding the macula is cured with low intensity burns, which aids in the treatment of macular oedema [18].
- Panretinal: This procedure is used to manage proliferative DR (PDR). It is completed in several sitting [18]. This cuts the chance of vision loss by at least half.

3.1 Medicine

- Intravitreal triamcinolone acetonide: Long-acting steroids such as Triamcinolone [18]. Studies have shown that people who are taking DME with intravitreal injection of triamcinolone improves the vision. The steroid decrease the macular oedema and improves the visual acuity [21]. This is not a permanent solution as it will last for 3 months.
- Intravitreal anti-VEGF: Periodic doses of intravitreal injection of anti-VEGF like bevacizumab and ranibizumab improves the visual outcome. It is less effective in cases with vitreous hemorrhage. This is the recommended treatment for present cases along with modified grid laser photocoagulation.
- Topical medication: There is not enough research to support the use of topical medicines, such as NSAIDs, in the macular oedema [22].

3.2 Surgery

In some cases, where laser surgery is not possible, vitrectomy is done. For example, in the case where blood is accumulated in vitreous. In this we remove the defective vitreous fill the space with a normal saline solution [23-25].

Early vitrectomy has proven to be in effect in people with insulin-independent diabetes. This is usually done under local or general anesthesia [26-30].

4. CONCLUSION

DR is a microvascular disease which is characterized by blurred vision, macular oedema, occlusion of retinal vessels etc. There are many theories for the pathogenesis of DR. Retinal structures are very much affected by hyperglycemia, inflammation, retinal neurodegeneration etc. A whole lot of risk factors are associated with the progression of DR. Risk factors such as hypertension, obesity, sex, hyperlipidemia, chronic kidney disease, smoking. These risk factors have either negative or indeterminate association with DR. But there are some risk factors which has a positive association with DR such as myopia. There are various signs and symptoms for the disease like blurred vision, impaired color vision, floaters, poor night vision, dark spot in center of vision etc.

DR leads to many complications such as vitreous hemorrhage, detached retina, retinal scar, glaucoma etc. There are great chances of management of DR until there hasn't been any permanent damage in retina. There is a chance of 95% to prevent loss of vision if DR is diagnosed at early stage or even in advanced stage given there is no permanent damage in retina.

For the diagnosis of DR there are various tests like testing of vision, dilation of pupillary apparatus, use of direct or indirect ophthalmoscopy, fundus fluorescein angiography (FFA), retinal vessel analysis, optical coherence tomography (OCT). There is a rising need for screening of DR for the early detection of the disease to decrease the incidence of the disease in various countries. UK has launched a program for the screening of DR which is conducted every year. Similar programs are needed in almost every countries as the population is more prone to the disease because of the sedentary lifestyle and increasing cases of diabetes.

A lot has been developed in the field of medicine to find a cure for DR. There are three main treatment options for the management of the disease. Although there is no cure of DR but several modes of management are Laser photocoagulation, Injection of steroids or anti-VEGF agents into the eye, Vitrectomy is the major treatment categories for the cure of DR. The surgeries are very dangerous as it can cause more damage if not performed carefully. It can cause retinal detachment, retinal scar which can lead to complete loss of vision. The medication is a safer option for the management but it is done on a periodic basis. And patient has to be compliant with the medication or else the disease will progress and will ultimately lead to complication. These techniques are very effective in controlling and we hope that medicine will evolve so that we can get a permanent

solution for the disease and one day the disease will be curable.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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