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Diabetic Retinopathy: Pathophysiology and Treatment

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A B S T R A C T

Diabetic retinopathy (DR) is the most common complication. It is has long been recognized as a microvascular disease. The DR is classified in to two types, those are NON-Proliferative DR, Proliferative DR, and macular Edema. The signs and symptoms like, blurred vision, vision loss, patches in eye. The pathophysiology involved mainly growth factors (VEGF) and glycation activaton (AGEs) cause neovsculariozation, the pathways mainly involved in this polyol path way, oxidative stress, protein kinase C activation, Non-enzymatic activity. The diagnosis ocular examination fundus photography, fundus flurosence angiography, optical chocherence, Ultrasonography are detect the diabetic retinopathy. The treatment is Aflibercept, Ranibizumb, these two drugs are approved by the U.S, FDAfor the treatment of diabetic retinopathy. Advanced treatment like Injectinto eye, laser therapy, vitrectomy.

Keywords: Diabetic retinopathy (DR), optical chocherence, Ultrasonography, laser therapy, vitrectomy

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Diabetes: Diabetes mellitus is derived from the Greek word, diabetes mean “Siphon” to pass through and the Latin word mellitus mean “sweet”. The term “Diabetes” was first used by Apollonious of Memphis around Diabetes 250 to 350 BC. Anicent Greek, India and Egyptian civilization discovered the sweet urine. Merigna and Minkowski, in 1889, discovered the role of the pancreas in the pathogenesis of diabetes.[1] Diabetes mellitus is a high level of glucose ,which in-adequate control of blood levels of glucose, and a disorder of metabolism where pancreas produce little or no insulin or the cells do not respond to the insulin produce. Glucose or sugar builds up in blood, over flow and is lost into urine. A blood sugar

levels less than 140mg/dl is normal. A reading is more than 200 mg/dl, after two hours indicates diabetes. A reading between 140 and 199 mg/dl indicates pre-diabetes. Diabetes mellitus classified into four types, those are Type1, Type 2, Gestational diabetes, Neonatal diabetes. Type 1 diabetes is insulin dependent diabetes, Type 2 diabetes is non-insulin dependent diabetes. Gestational diabetes mainly seen in pregnancy women. Neonatal mostly shows effect in children[1,3].

Diabetes retinopathyis a diabetes complication that affects eye. It is damage to the blood vessel s of the light-sensitive tissue at the back of the eye (retina). At first, diabetic retinopathy might cause no symptoms or only mild vision problems. Diabetic retinopathy is a micro vascular disorder. Which occurs and a long term of diabetes mellitus .which leads to loss of vision and blindness. Diabetic retinopathy is progressive dysfunction of the retinal blood vessel caused by chronic hyperglycemia. Initially it is asymptomatic, if not treated, It is causes low vision and blindness. Diabetes retinopathy is common cause of sever vision loss in adult of working age groups in the western world. Globally 30% of peoples suffering from diabetes retinopathy. DR clinically manifestation of vascular abnormalities in the retina[4,6].

Diabetic retinopathy is divided into two types. Those are Non-proliferative diabetic retinopathy, proliferative diabetic retinopathy. The number of patients with DR in America is estimated to reach 16.0 million 2050, with the vision treating complication affecting around 3.4 million of them. NPDR (non-proliferative diabetic retinopathy) represents the early stages of DR, where in increased vascular permeability and capillary occlusion in retina. During this stage retinal pathologies including microaneurysms, retinal haeomorrhage can detected by fundus photograpy although the patients may be asymptomatic.

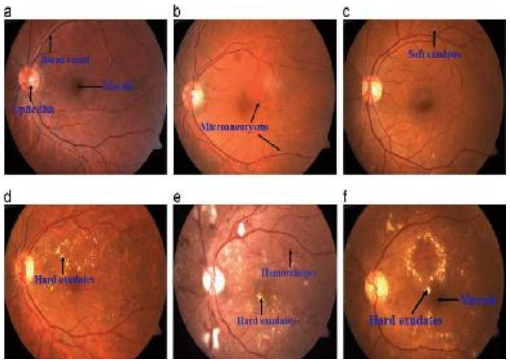
PDR(proliferative diabetic retinopathy) occurs with further retinal ischemia and is characterized by the growth of new blood vessels on the surface of the retina or the optic disc. These abnormal vessels may bleed, resulting in vitreous hemorrhage, subsequent fibrosis, and tractional retinal detachment. PDR is more advanced stage of DR, it is characterized by neovascularization.Thesestage, the patient may experience severe vision impairment when the new abnormal vessels bleed into the vitreous. The most common cause of vision loss in patient with diabetic macular edema[6].

Uncontrolled diabetic can be lead to many ocular disorders like cataract, glaucoma, ocular surface disorders, recurrent stye, non-arteritic anterior ischemic optic neuropathy, diabetic papillopathy, and diabetic retinopathy, out of which diabetic retinopathy is the most common and severe ocular complication. Poor glycemic control, uncontrolled hypertension, dyslipidemia, nephropathy, male sex, and obesity are associated with worsening of diabetic retinopathy. Recent work indicates that diabetes markedly impact the retinal neovascular unit and its interdependent vascular, neuronal, glial, and immune cell[4].

2. Sings and Symptoms

In early stages of DR we can obsere changes In their vision, like trouble reading or seeing farway objects these change come and go. In later stage of the disease, blood vessels in the retina starts to bleed into the vitreous. If this happens, patient may see dark, floating spots or streaks that look like cobwebs.[5,6]

- Poor night visio
- Blurred vision
- New color blindness
- Small dark spots
- Streaks in eye
- Trouble reading or seeing far way objects
- Impaired color vision
- Patches or streaks that bock person



Causes

Diabetic retinopathy is a complication of diabetes. It causes high blood sugar levels, which can damage blood vessels. The damged veseels in theretina can leak fluid, protein, and fats, formiing deposits that can interfere with vision. The damged blood vessels are not as effective at carrying oxgen to the retina. Hpertensive retiiinopathy is a complication of high blood pressure that usually takes many years to develop. High blood pressure damage the blood vessel walls, casuiing them to thicken and narrow. This reduces the blood supply available to the retina, leading to retinal damge. Eventually, blood can leak in to the retina, causing further damage**.**

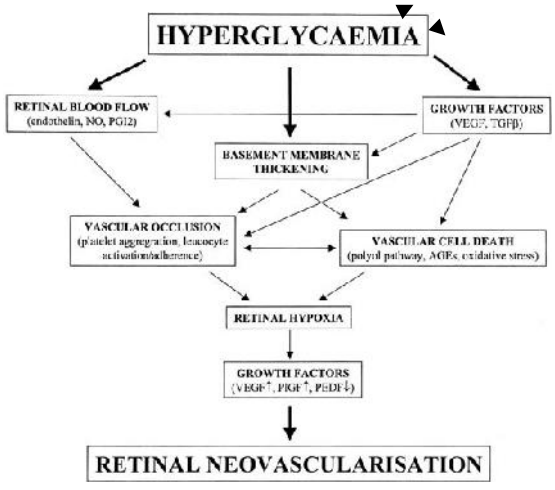
Diabetic retinopathy is caused by high blood sugar due to diabetes. Over time having too much sugar in blood ,it can damage retina the part of eye that detects light and signal to brain through a nerve in the back of eye. Common causes are diabetic and hypertension (high blood pressure). Diabeticcausehigh blood sugar levels, which can damage blood vessels. [5][6]

Risk Factors

Anyone who has diabetes can develop diabetic retinopathy, the risk factors of developing the eye condition can increases as a result of

- Poor control of blood glucose level
- High blood pressure
- High cholesterol
- Tobacco use
- Pregnancy
- Obesity
- Dyslipidemia
- Nephropathy
- Oxidative stress
- Genetic factors
- Hormonal imbalance
- Adiponcetin
- Apolipoprotein
- Inflammation s
- Puberty [6]
- Pathophysiology

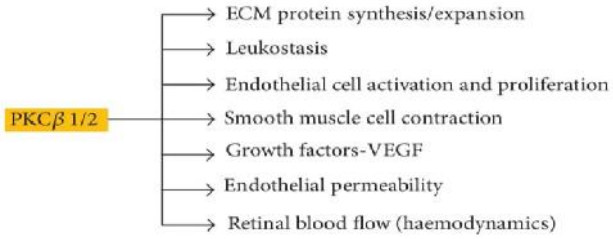
Chronic hyperglycemia to be the primary pathogenic agent in DR(as described by UKPDS and DCCT). Hyperglycemia leads to the activation of alternative pathways of glucose metabolism, including the polyolpathway, oxidative stress, protein kinase Cactivation, non-enzymatic protein glycation leading to advanced glycation end products (AGEs). The end results of these alternative pathways is the activation of cytokines along with growth factors and vascular endothelial dysfunction, which eventually leads to increased the vascular permeability and microvascular occlusion. Retinal ischemia, which occurs as a consequence of microvascular occlusion, leads to the formation of IRMA (intraretinal microvascular abnormalities) and neovascularization. [11][12].



In the polyol pathway, glucose is reduced to aldose reductase enzyme. The permeability of Sorbitol leads to its accumulation in all retinal cell to osmotic damage of the cells. Also, the use of NADPH (reduced nicotinamide adenine dinculeotide phosphate) during the reduction process leads to further oxidative damage. [15][16][17].

Oxidative stressis a results of reactive oxygen species (ROS) leading to cell and tissue damage.[24][25]26].

Protein kinase C is involved in signal transduction. Its activation leads to basement membrane alternation along with vascular changes like increased vascular permeability, the release of angiogenic growth factors, vascular stasis, and capillary occlusion.[20][21][22].



In non-enzymatic protein glycation, reducing sugars react with free amino acids of nucleic acid, proteins, and lipids leading to the formation of advanced glycation endproducts that are responsible for alteration in extracellular matrix proteins.

The morphological changes seen in smallretinal vessels in DR includes early loss of pericytes, basement membrane thickening loss of endothelial cells, increased vascular permeability, platelet aggregation, leukostasis, and capillary dropout.[14][17].

Diabetic retinopathy does not only affect the microvessels of the retina but also the Muller cells, which are the primary glial cells of the retina. Function of Muller cells are maintaining the structural integrity of the retina, regulation of the blood-retinal barrier and protein blood flow, uptake and recycling of various neurotransmitter, retinoic acid compound, and ions (such as potassium K), regulation of metabolism and supply of nutrients to the retina. In diabetes, there is downregulation of kir channel because of which there is continued potassium uptake leading to swelling of Muller cells, which leads to Muller cells, cell dysfunction. Fluid accumulation inside the Muller cells is responsible for DME [18][19]. Hyperglycemia leads to release of Growth factors such as

- Vascular endothelial growth factor (VEGF),
- Pigment epithelium –derived factor (PEDF),

- Platelet –derived growth factor (PDGF),
- Basic fibroblast growth factor (BFGF or FGF2)
- Insulin-like growth factor (IGF),
- Hepatocyte growth factor / scatter factor (HGF/SF),
- Placenta growth factor (PGF),
- Erythropoietin
- Angiopoietin-2

Cytokines and chemokines including

- Interleukin-1β
- Interleukin 6
- Tumor necrosis factor-α
- Chemokine ligand-2 [19]

DIAGNOSIS:

Ocular examination

The patient should be thoroughly tested for:

- Visual acuity,
- IOP measurement,
- Gonioscopy (forneovasulartion ofirish/angels and for raised intraocular pressure/iop),
- Slit-lamp examination (to rule out other ocular manifestation of diabetes mellituDilated fundus examination with +70 or +90 D lens for posterior pole (on slit lamp)and with +20 or +28 D lens for detailed peripheral examination (with an indirect ophthalmoscopy) and diabetic retinopathy grading should be done.
- The following additional posterior segment investigation should be done for Conformation of the diagnosis of diabetic retinopathy [7].

Fundusphotography:

- For documentation and record purposes.
- It is a very helpful tool for patients education, as well.

Fundus fluorescein angiography (FFA)

- For the diagnosis of ischemia maculopathy.
- To locate capillary dropout areas.
- To different IRMA from neovascularization.
- To different disc collaterals from disc neovascularization.
- To reveal occult new vessels that could not to be detected on clinical examination.
- To find out the cause of unexplained visual loss.

Optical coherence Tomography (OCT)

- To evaluate retinal thickening
- Assessment and monitoring edema after initiation of treatment
- Very helpful markers to plan for the next sitting of intravitreal injection.
- To diagnosis Vitreomacular traction (VMT) and the epiretinal membreane (VMT).

Ultrasonography (Bscan)

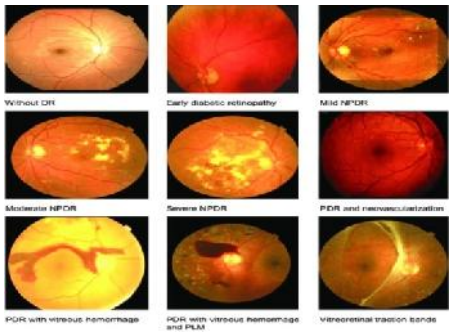
- Which might require surgery (pars plans vitrectomy).

It is a very useful tool in hazy media for diagnosis of

- Vitreous hemorrhage
- Tractional retinal detachment
- Subhyaloid hemorrhage
- Posterior vitreous detachment.

Optical Coherence Tomography Angiography (OCTA): OCTA employes motion contracts imaging to retinal blood flow, generating images that are similar to fluoresce in angiography without injecting the dye invasively.

- Provides detailed information of the retinal vasculature.
- Helpful for demarcation of foveal avascular zone helping to find out foveal ischemia.



- To delineate capillary of drop out areas.
- Accurate detection of even mild IRMA.
- Vascular sings like looping, beading, dilatation can very well be appreciated on OCTA.
- The earliest etection of microvascular changes (before the visibility of microaneurysm).
- Especially useful in patients with kidney disease and patient prone to an anaphylactic reaction to the dye.

3. Treatment

Treatment, which depends largely on the type of diabetic retinopathy patient have and how sever it is, is geared to slowing or stopping the progression. General systemic control of diabetes

- Strict metabolic control of diabetes.
- HbA1C levels should be kept under the 6.5.[27][28]

- Lifestyle modification like routine exercises and proper diabetic food diet.
- Patient should visit diabeteologists for proper follow-up visit should take timely diabetes medication.
- Other systemic ailments like hypertension, dyslipidiemia, hypoprotiennemia, anemia, nephropathy, cardiac aliments, and others should be also taken care of by respective medications.

(A)Management of Non-proliferative Diabetic Retinopathy: Strict glycemic control and strict complication of patients towards antidiabetic medication is the key to manage a case of NPDR. Stress should be on proper systemic control of diabetes mellitus,keeping a watch on the progression of ocular findings. Associated comorbidites should be taken care of A detailed systemic investigation by a physician or an endocrinologist should be done to rule out any other systemic side effects of diabetes mellitus.

- Very mild NDPR- follow-up ever yearly.
- Mild to moderate NDPR- follow-up6-12 monthly. 16% cases of mild NDPR and 23% cases of moderate NDPR progress to proliferative stages within four years.
- Severe to very severe NDPR- cases follow-up 2-4 months. 50% of severe NDPR and 75% of cases of very severe NDPR progress to PDR within one year.[31].

(B) Management of Diabetic Macular Edema

Center involving diabetic macular edema- now days, anti-VEGF agents have become the first line treatment center involving diabetic macular edema. Bevacizumab, Ranibizumb, and Aflibercept have shown to have beneficial effects in patients with baseline better visual acucity. Aflibercept is shown is have better visual outcomes in patients with worse baseline visual acucity. Recently, Aflibercept and Ranibizumb have received FDA approval for use In diabetic retinopathy associated with macular edema. Non-center involving macular -focal or Grid laser-guided by ETDRS is the treatment of choice [32][33][34].

Nowadays, in the era of anti-VEGF medication, laser treatment is usually avoided in the center involving macular edema. It may be added as adjuvant therapy in patient not responding to anti-VEGF therapy alone. From the results of the DRCR network (diabetic retinopathy clinical research), it was found that monthly loading doses of Ranibizumb followed by prove re nata or PRN schedule (as and when needed) have better results in center involving macular edema than single therapy with laser or steroids alone. As stated by ETDRS, laser helped in halting the progressive of moderate visual loss, but it did improve the visual acuity.

Bevacizumab intravitreal injection is also effevtive in the center involving DME, but it is not FDA approved. Hence it is available only as an off table use. Cluster endophthalimits due to fake drugs or other reasons is another concern[35]. DRCR network also studied the role of aflibercept in DME, and it was found to be useful in patient with initial worse visual acuity(protocol T of DRCR.net [32]).other notable studies other than DRCR network on intraviterial anti-VEGF injection include RISE, RIDE, READ,RESTORE, BOLT, and RESOLVE.[33][35]. Doses of commonly used intravitreal injection:

- Bevacizumab-1.25mg/0.05ml (PACORES, DRCR.net PROTOCOL H, BOLT, READ-2[36] [37][38][39].
- Ranibizumab -0.5mg or 0.3 mg/0.05 m (RESLOVE, DRCR.net PROTOCOL I, RESTORE, RISE/ RIDE [40][41][42][43][44][45].
- Afliberceept-2mg/0.05 ml (DA VINC, VISTA/ VIVID, DRCR.net PROTOCOL T) [45][46][47].
- Pegaptanib – 0.3mg/0.9 ml[not FDA approved for this indication] (Cunninham et al,Sultan et al). [48] [49] [50].

(C) Treatment Proliferative Diabetic Retininopathy

Prognosis is guarded in patients of advanced diabetic eye disease. Persistent vitreous hemorrhage can initially be givenm the retinal of intraviterial injection of anti-VEGF following which if the hemorrhage resolves, then scattered pan-retinal photocoagulation in the visible areas can be tried. Ultrasnogram must exclude retinal traction if such an approach is considered. [51][52].If the hemorrhage does not resolves with the above management, pars vitrectomy should treatment of choice.

Advanced diabetic retinopathy:

If patient have proliferative diabetic retinopathy or mcular edema, patient will need prompt treatment. Depending on the specific problems with patient retina, option might include

Injecting medication into the eye;

These medication, called vascular endothelial growth factor inhibitors, are injected into vitreous of the eye. They help stop growth of new blood vessels and decrease fluid buildup two drugs are approved by the U.S. For Drug Administration (FDA) for treatment of diabetic macular edema-Ranibizumab (Lucentis) and Aflibercept (Eylea).A third drug, Bevacizumb (Avastin), can be used off-label for the treatment of diabetic macular edema. These drugs are injected using topical anesthesia. The injection can cause mild discomfort, such as burning, tearing or pain for 24 hrs after the injection. Possible side effects include a buildup of pressure in the eye and infection.These injections will

need to be repeated. Some cases, the medication is used with photocoagulation.

Photocoagulation

This laser treatment, also known as focal laser treatment, can stop or focal laser treatment, can stop or slow the leakage of blood and fluid in the eye. During the procedure leaks from abnormal blood vessels are treated with laser burns.

Panretinal photocoagulation

These laser treatment also known as scatter laser treatment can shrink the abnormal blood vessels. During the procedure, the areas of retina away from the macular are treated with scattered laser burns. The burns cause the abnormal new blood vessels to shrink and scar.

Vitrectomy

This procedure uses a tiny incision in patients eye to remove blood from the eye (vitreous) as well as scar scar tissue that's tuging on the retina. It is done in a surgery center or hospital using local or general anesthesia.

4. Conclusion

Although the incidence of DR continues to increase, the past decade has seen the emergency new treatment options, especially drugs targeting VEGF, which have greatly improved our management of DME and PDR endpoints. Never the less, a presenting need remains for efficacious new treatment for all stages of DR, and this under prins continuing efforts to fully understand the coex ways in which diabetics impact the retina. An important conceptual advance has been the recognition that DR is a disease of the neurovascular unit, with multiple, interdependent cell type contributing to dysfunction of the retina. New therapeutic approaches should adopt this more holistic view of how diabeties affects the retina and tailor appropriate treatment to more precisely define disease phenotypes with exciting prospect of achieving successful clinical outcomes for all patients.

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