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Current and Emerging Therapies for the Management of Diabetic Retinopathy

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ABSTRACT

Diabetes Mellitus (DM) has many complications, in which Diabetic Retinopathy (DR) is the major one. Blindness among working age people was due to DR. Retinal angiogenesis and retinal vascular permeability is the pathogenesis behind vision loss. Polyol pathway, protein kinase C (PKC) activation, renin angiotensin-aldosterone system (RAAS), oxidative stress etc are the pathophysiological pathways which are discussed in this review for better understanding. PKC inhibitors, anti-inflammatory agents, RAAS blockers, anti-vascular Endothelial growth factor (VEGF) agents, antioxidants and fibrates which are the used for the better treatment for DR is also elaborated in this review.

INTRODUCTION

DM is characterized by high levels of blood glucose which is the disorder of carbohydrate metabolism (King *et al*., 1998). Globally, 387 million people had diabetes in 2014 and its prevalence will increase to 592 million individuals by 2035 as per International Diabetes Federation (Diabetes Federation., 2014). According to World Health Organization (WHO) diabetes is defined as a chronic disease in which enough insulin was not produced by the pancreas or the body does not take enough insulin. DR was caused by a sustained increase in glucose level and consequences in minor vascular retinal vessels (Porta and Bandello, 2002). DR may be characterized by the hypoxia (abnormal blood vessel growth) in the retina (Rechtman *et al*., 2007). DR is not only chronic disease, but also it is a sight threatening disease of retinal vasculature (NICECKS., 2010).

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The pathogenesis behind this blindness may increase retinal vascular permeability and retinal angiogenesis. These changes are due to hypoxia and chronic hyperglycemia. If the diagnosis was done with proper timing and retinal laser treatment, blindness can be reduced in 90% patients. For avoiding DR and slowing down its progression, prevention of DM and good metabolic control is more important (ETDRS, 1991).

There are two different types of DR. Polyol pathway, non-enzymatic glycation, PKC, inflammatory, hemodynamic changes, growth factor, oxidative stress and renin angiotensin pathways are pathological pathways which leads to DR. DR can be also prevented by controlling blood sugar levels and blood pressure. Various approaches to treat DR are PKC inhibitors, RAAS inhibitors, Anti-VEGF inhibitors, Fibrates, antioxidants and anti-inflammatory agents as well. As conventional therapy has limitations for DR treatment there are certain therapies that are emerging for the treatment that includes laser therapy, vitrectomy and intra-vitreal injections of anti VEGF agents, corticosteroids and certain other pharmacological agents as well.

In DR, combination therapy was used rather than monotherapy that intra-vitreal injection of one or two drugs has given to the patient who has undergone vitrectomy surgery for proliferative diabetic retinopathy (PDR). So there is a stronger support for combination therapies than monotherapy. This paper reviews about DR mechanisms, new emerging therapies and various approaches for the management of the disease.

Pathogenesis of Diabetic Retinopathy

DR may cause visual acuity (VA) because it is a microvascular complication of diabetes, which leads to vision loss. Increased blood sugar can damage retinal blood vessels. Swelling of retinal tissue and clouding of vision was due to leakage of blood and other fluids. Cotton wool spots, capillary closure, arterio venous shunts, neovascularisation, retinal haemorrhage, retinal exudates/oedema, lipid exudates and macular edema are the clinical symptoms of DR. Vascular permeability was also increased which leads to retinal thickening and loss of visual acuity. DR was managed by controlling hyperglycemia, hypertension and dyslipidemia. EDTRS classified DR as follows:

Non-proliferative* retinopathy *(NPDR)

It is more extensive than background retinopathy. Blood flow becomes restricted, but did not show any new blood vessel growth.

Mild NPDR

Micro-aneurysms (secular enlargement of the venous end of a retinal capillary)

***Moderate NPDR*:** Between mild NPDR and severe NPDR

Severe NPDR

Severe intra-retinal haemorrhages and micro-aneurysms

Proliferative retinopathy (PDR)

Growth factors are the chemicals which are released when blood vessels of retina damages, this leads to growth of tiny blood vessels (proliferate) from the damaged blood vessels.

The major reason for DR complication is hyperglycemia. Metabolic dysfunction increased by high glucose level and other signalling pathways activation leads to DR progression. At present, DR represented by glycemic control which is the most effective medical treatment (Hudson, 1996; Aiello, 2003; Porta and Allione, 2004; Wang *et al*., 2009). There are Studies which showed that blood sugar level control is more important (Schaumberg *et al*., 2005; Kilpatrick *et al*., 2006). It was found that more recent pathogenesis behind diabetes complications are poly (ADP-ribose) polymerase (PARP), reactive oxygen and inflammatory cascade mechanisms are involved in the (Stratton *et al*., 2006). Rather than oxidative stress and PARP activation increased aldose reductase activity is a major cause in the pathogenesis of diabetes (Obrosova *et al*., 2005). There are many biochemical pathways involved in the DR progression. They may include: polyol pathway, non enzymatic glycation, PKC activation, hemodynamic changes, RAAS system, subclinical inflammation, leukostasis, oxidative stress and growth factors. Schematic diagram of pathogenesis of DR was shown in Fig1:

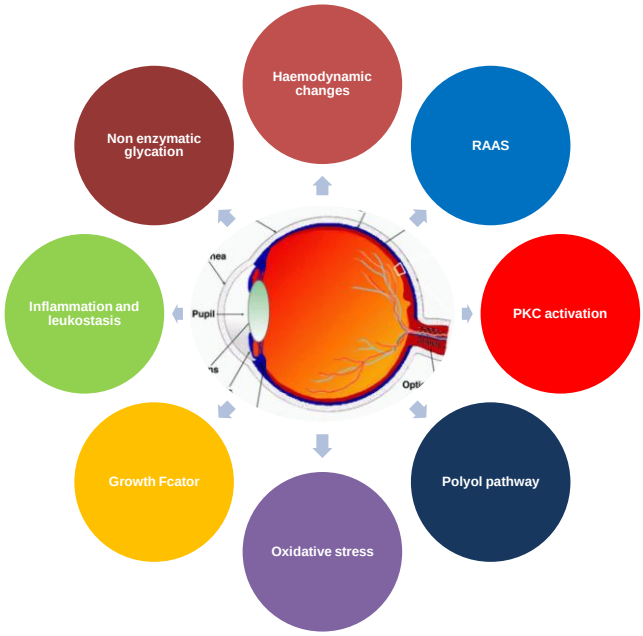

Fig. 1: Pathogenesis of DR.

Polyol pathway

Certain amount of glucose is metabolized in cellular metabolism by polyol pathway. Glucose flux is increased by this pathway in diabetes patients. Polyol pathway is controlled by the two steps. In the polio pathway, aldose reductase helps to reduce sorbitol from glucose using NADPH, and then sorbitol dehydrogenase is an enzyme that metabolizes sorbitol to fructose, which uses NAD+ as a cofactor (Dagher *et al*., 2004). If an excess of sorbitol in retinal vascular cells cause osmotic damage leads to DR. In order to predict individual susceptibility in retinopathy, aldose reductase gene polymorphisms may be helpful. Even though aldose reductase inhibitors (ARIs) have yielded incompatable results in DR of experimental animals polyol pathway has become a dread target (Hammes *et al*., 1991).

Non-enzymatic protein glycation

AGEs are important pathogenic mediators which reduce sugars, by non-enzymatic reaction. Diabetic patients have AGEs in their retinal vessel, same as in serum and retinopathy. Cells get affected by AGEs by three mechanisms: (a) adducts which is present on altered serum proteins, (b) glucose metabolism product endogenous adducts, and (c) ECM-immobilised structural modification of proteins. Amadori product is formed as a result of early glycation and oxidation. AGEs is generated by protein and lipid glycation. AGE formation and activation of AGE receptors represent important as per early experimental works. In DR, inhibition of these pathways with interconnected pathogenic mechanisms presents a valid avenue for therapeutic exploitation

(Chibber *et al*., 1999; Stitt *et al*., 2002; Peppa *et al*., 2003; Wang *et al*., 2006; Zong *et al*., 2011).

PKC Activation

It helps in cell signalling. Hyperglycemia leads to increase in the de novo synthesis of di-acylglycerol (DAG), which causes major changes in endothelial permeability, hemodynamic changes, extracellular matrix protein synthesis, intracellular changes and VEGF production (Koya and King., 1998; Clarke and Dodson., 2007). The PKC β1/2 isoform expression contributes to the loss of capillary pericytes. Inhibition of PKC only reduces the loss of vision, not for preventing DR (Simonson 1988).

Hemodynamic changes

The mechanism for DR progression has increased blood flow in the retina and loss of auto regulation. It has documented that the diabetic patients have a high incidence of hypertension (Kohner., 1993; Mancia., 2005). Hypertension contributes to DR progression by two mechanisms. First, the endothelial dysfunction occurs by mechanical stretch and shear stress on the endothelial cells (Berka., 2006). Second, regulation of blood pressure in the endocrine system was involved in the pathogenesis of DR (Funatsu *et al*., 2002).

RAAS

RAAS involved in the maintain body fluid balance and regulates blood pressure. During PDR, the expression of the receptors, signalling molecules of the RAAS and angiotensin receptors increases in the retina (Funatsu *et al*., 2002; Sjølie *et al*., 2008). The DR Candesartan Trials (DIRECT) and RASS both reported with the reduction of retinopathy progression (Van Hecke *et al*., 2005; Chaturvedi 2008; Mauer *et al*., 2009).

Subclinical inflammation and leukostasis

Retinal inflammation causes increased intraocular blood pressure eNOS, new blood vessels formation and VEGF leads to haemorrhages in the retina which causes increased permeability and leukostasis. (Lutty *et al*., 1997). Inflammation is due to increase in the serum concentration of cytokines, adhesion molecules and activation of immune cells (Schroder *et al*., 1991; Spijkerman *et al*., 2007; Klein *et al*., 2009).

In DR pathogenesis leukostasis leads to capillary occlusion and ROS associated apoptosis (Halliwell and Gutteridge., 1990).

Oxidative stress

Oxidative stress is lack of proportion between ROS production and ROS neutralization by antioxidants. The cellular components are damaged by oxidative stress and leads to the pathogenesis of many diseases. ROS are detoxified in normal physiological conditions (Mates *et al*., 1999). Increased oxidative species causes DR progression (Enden *et al*., 1995).

Growth factors

Growth factors which contribute DR development includes basic fibrobroblast growth factor (bFGF) (Armstrong *et al*., 1998), insulin-like growth factor-1 (IGF-1) (Hueber *et al*., 1996; Haurigot *et al*., 2009), angiopoietin- 1 and -2 (Patel *et al*., 2005; Berka *et al*., 2006; Rangasamy *et al*., 2011), stromal-derived factor-1 (Coxon *et al*., 2010), epidermal growth factor (EGF) (Lev-Ran *et al*., 1990), transforming growth factor-beta 2 (TGF-$\beta\beta$2) (Min *et al*., 2006), platelet-derived growth factors (PDGFs) (Praidou *et al*., 2009), and erythropoietin (Eckardt, 2009). Among these growth factors VEGF plays an important role in DR pathogenesis.

The DR leads to two visual complications, (i.e.,) diabetic macular edema (DME) and PDR. Standard treatments for DME and PDR are glycemic control and photocoagulation. In recent years, there are certain measures to avoid the risk for blindness which includes medical managements and ocular managements. An adjunctive pharmacologic therapy by anti-VEGF agents and triamcinolone acetonide shows better treatment for both PDR and DME. There are some new factors involved in the pathogenesis of DR, emerge to the new therapies.

Currently approved therapies

The therapies that are currently available for the management of DR. Laser treatment, vitrectomy surgery, anti-VEGF agents and corticosteroids are the therapies that are available presently in the market for the treatment of DR.

Laser Treatment

Laser treatment depends on the disease severity. Laser photocoagulation was more effective for the treatment of DR. There are two types of laser treatment.

Scatter or pan retinal photocoagulation

Small amount of laser has been needed to treat DR. Laser should not be applied to the central part of the retina.

Focal laser photocoagulation

Laser photocoagulation leads the hypoxic condition in retina to anorexia.

Vitrectomy surgery

Complications of DR may be the interactions between the vitreous and retinal surface. Here vitreous gel is removed from the centre of eye. Local or general anaesthesia are used to stop bleeding from vitreous. In order to carryout vitrectomy, it needs overnight hospital stay. Eyes may take weeks to get recovered after treatment. Inflammation and infection is reduced by applying eye drops. If both eyes require vitrectomy, after the first eye has recovered second eye will be treated again (Harbour *et al*., 1996; Smiddy and Flynn., 1999; DRCRNWC., 2010).

Anti VEGF Treatment

Anti-VEGF agents were helped in the retinal vascular permeability improvement, causes blood-retinal barrier break-down, and finally results in retinal edema (Aiello *et al*., 1997). VEGF level is increased in DR. There are known 5 isoforms of VEGF. At present, pegaptanib (Macugen; Pfizer, Inc., New York, USA), (Cunningham *et al*., 2005; Gonza´ lez *et al*., 2009), ranibizumab (Lucentis®; Genentech, Inc., South San Francisco, California, USA) (Chun *et al*., 2006; Rosenfeld *et al*., 2006; Erfurth *et al*., 2014; Comyn *et al*., 2014), bevacizumab (Yanyali *et al*., 2007; Roh *et al*., 2008; Fang *et al*., 2008;) (Avastin®; Genentech, Inc.), and VEGF Trap-Eye (Do *et al*., 2009; -108) (Regeneron Pharmaceuticals, Inc., Tarrytown, New York, USA).

Corticosteroids

Corticosteroids are used for various intraocular neovascular and edematous diseases, which includes certain diseases such as DME, PDR, neovascular glaucoma and chronic prephthisical ocular hypo tony (Paccola *et al*., 2008).

Emerging therapies

Treating DR was done by initiation of some of the biochemical mechanisms, the drugs which includes are aldose reductase inhibitors, PKC inhibitors, anti-inflammatory drugs, fenofibrate, somatostatin analogs, RAAS blockers, anti-oxidants and certain combination therapies.

Aldose reductase inhibitor

Newly developed inhibitors addressed more efficient action than older but in clinical testing which showed failure in the better management of DR (Sun *et al*., 2006).

PKC Inhibitors

When vascular endothelial cells were exposed to oxidative stress PKC activity also has been increased, which leads to the development diabetic micro vascular complications. Endothelial cell permeability, blood flow and angiogenesis are regulated by PKC (Taher *et al*., 1993; Huang *et al*., 1997).

Table 1: List of drugs and therapies that are currently available in the market for DR treatment.

Drug/ Therapy	Mechanism of action	Grade	Number of patients examined	Study Type	Outcomes	Phase
Laser	Destruction of retina and supply oxygen, reduction in VEGF expression	PDR and NPDR	60	Interventional	Incidence of vision loss after 1 yr.	Phase 3
Vitrectomy surgery	Surgical removal of vitreous gel	PDR	347	Randomized	Persistent haemorrhage were evaluated	Phase 3
		PDR	70	Randomized	Intraoperative bleedings and intraoperative retinal breaks was measured.	Phase 2
Anti-VEGF agents	Pegaptanib (Inhibits the VEGF from binding and activating the VEGFR2 receptor)	PDR	30	Non-Randomized	To further establish the efficacy of intra-vitreal injections in the regression of retinal neovascularisation secondary as compared to laser.	Phase 4
	Bevacizumab (It binds and inhibits the all isoforms of human VEGF activity	Severe NPDR	40	Non-Randomized	Evaluated Visual Acuity, neovascularisation leakage points and florescent angiography	Phase 2 & Phase3
	Ranibizumab (Inhibits VEGF A and activating the VEGF 2 receptor	PDR	20	Randomized	The improvement or worsening of vision was measured	Phase2
	Aflibercept (Have VEGF binding sites)	PDR	20	Randomized	Incidence and severity was measured	Phase2 & Phase3
Corticosteroids	IVTA (Down regulating matrix metalloproteinase activation)	PDR	60	Randomized	Visual acuity, no of treatments, duration of efficacy was measured	Phase1
	Fluocinolone acetonide (Inhibition of VEGF and anti-inflammatory properties)	DR & DME	40	Randomized	Between group difference in mean visual acuity change	Phase2
	Dexamethasone (PKC activation)	PDR	100	Randomized	Reoperation was needed	Phase2

Table: 2: Emerging therapies for the better management of DR.

Category	Drug	Mechanism of action	References
Aldose reductase inhibitors	Aspirin	Reduce VEGF expression	(Sun *et al*., 2006)
PKC inhibitors	Ruboxistaurin mesylate	Inhibitor of PKC-1 and 2 receptors	The PKC-DRS group., 2005
	Pazopanib	selective inhibitor of glycation that leads to inhibition of VEGF and PEDF	Thakur *et al*., 2011
Anti-inflammatory	Etanercept, Fidarestat	Intercellular adhesion molecule1 (ICAM1) expression can be reduced	Tsilimbaris *et al*., 2007, Kato *et al*., 2009
	Infliximab	Block the inflammatory molecule tumour necrosis factor α (TNFα).	Sfikakis *et al*., 2010
	ESBA105	Anti TNFα	Ottiger *et al*., 2009
Fibrates	Fenofibrate	VEGF inhibition, reduction of cytokines levels, PKC activation	Cheung and Wong., 2008
Somatostatin analogs	Octreotide	PKC activation	Grant *et al*., 2000
RAAS inhibitors	Valsartan	Angiotensin I (ATI) receptor antagonist	Satofuka *et al*., 2009 The EUCLID Study Group. 1997
	Lisinopril	Angiotensin-converting enzyme blocks rennin-angiotensin system	
	Candesartan	Angiotensin receptor blocker	
	Losartan	ACE inhibition	
Anti-oxidants	Ascorbic Acid	Stimulates the retinal GSH reductase and SOD activities inhibition	Chen., 2009
	Curcumin	Inhibition of VEGFs production	
	Vitamin E	Prevention of lipid per oxidation	
	Lipoic Acid	Reduction of VEGF expression	Clinicaltrials. Gov., 2016
	Resveratrol	Reduction of retinal oxidative stress	Kim *et al*., 2012
Combination therapies	Triamcinolone Acetonide	Intra-vitreal injection + Laser	Gillies *et al*., 2011
	Bevacizumab + Triamcinolone	Intra-vitreal injection	Paccola *et al*., 2008; Shimura *et al*., 2008;
	Ranibizumab + Triamcinolone Acetonide	Intra-vitreal injection + Laser	
	Bevacizumab	Intra-vitreal injection + Laser	Huang *et al*., 2009; Cho *et al*., 2009
	Pegaptanib	Intra-vitreal injection + Laser	Clinical trials Gov. 2015
	Aflibercept	Intra-vitreal injection + Laser	Clinical trials Gov. 2015
	Ranibizumab	Intra-vitreal injection + Laser	Brown *et al*., 2006

Anti-Inflammatory Agents

Intraocular inflammation is the second mechanism for the DR development. For this reason non steroidal anti-inflammatory (NSAIDS) agents were used for prostaglandins production inhibition (Sfikakis *et al*., 2005; Tsilimbaris *et al*., 2007).

Fibrates

Fibrates are lipid-lowering drugs which have been used often in dyslipidemia treatment. Reduction in total cholesterol, LDL, glycerides and increase in HDL levels are due to activation of alpha receptor (Keech *et al*., 2007; Dodson 2009).

Somatostatin analogues

Somatostatin is also known as a growth hormone inhibitor. It exists in two forms, one form has 14 amino acids and other has 28 amino acids. It shows that somatostatin prevents PDR progression, haemorrhage and it was used in laser and vitrectomy surgery in DR (McCombe *et al*., 1991; Grant *et al*., 2000; Boehm *et al*., 2001; Davis *et al*., 2001)

RAAS blockers

RAAS is involved in DR pathogenesis. Studies reported that increased levels of rennin, pro renin, and angiopoietin 2 (Ang 2) in the vitreous in patients with DR. As RAS blocker therapy may improve the condition of DR patients (Satofuka *et al*., 2009).

Antioxidants

Increase in oxidative stress due to hyperglycemia leads to high glucose level and other metabolic abnormalities. This results in the ROS overproduction. When there is no balance between their production and destruction it results in oxidative stress. The ROS formation was mediated by both enzymatic and non-enzymatic mechanisms. These are the some of the important antioxidants that are currently being studied (Bursell *et al*., 1999; Garcia-Medina *et al*., 2011; 139-141).

Cryotherapy (Freezing)

It may help in DR treatment. Laser can be performed after blood in vitreous layer settles down. In some cases retinal blood vessels may shrink and retina is bonded back of the eye.

Combination Therapies

Combination therapy has yielded better results than intra-vitreal monotherapy. The RESTORE study (SchmidtErfurth *et al*., 2014) showed a greater improvement in patients treated with both intra-vitreal and laser than in patients treated with monotherapy.

Similarly, several studies reported an increased likelihood of an improvement in BCVA from baseline in patients treated with IVTA and laser versus only laser at 2 years. On the other hand, the READ2 study reported no significant difference in visual outcomes in the combination therapy group (Nguyen *et al*., 2010), although combination treatment provided an improvement in BCVA and a greater decrease in macular edema with fewer injections.

Future Therapies

The future DR treatment relies not only on the development of medications targeting molecules to the DR pathogenesis, but also on the development of novel delivery techniques. In order to maximize the effect of the treatment and minimize systemic adverse effects, targeted delivery of medication to the retina was ideal. Data's are emerging that medicine which is administered as eye drops are able to reach the retina than any other formulation with better therapeutic concentrations. Future development for therapies for DR treatments includes hepatocyte growth factor, matrix metalloproteinase-9 (MMP9), monocyte chemo tactic protein1 (MCP1), kallikrein, Ang2, and NFkB. Inhibition of hepatocyte growth factor and MMP9 may prevent DR or cause regression of PDR. Retinal neovascularisation was suppressed by NFkB inhibition (Yoshida *et al*., 1999). Retinal vascular permeability improvement was associated with Ang2 (Rangasamy *et al*., 2011), Kallikrein activation (Feener., 2010) and Hepatocyte growth factor (Nishimura *et al*., 1998).). Increased level of MMP9 has been found in vitreous and retina of patients with diabetes (Jin *et al*., 2001).

DR and PDR regression can be prevented by these two molecules. As the exact mechanisms involved in the pathogenesis of DR are elucidated more therapeutic targets will emerge, and the armamentarium of treatment options for DR will expand greatly.

CONCLUSION

DR is which may lead to legal blindness and it is a major public health problem. Early detection through screening, educating the population and timely intervention may decrease the complications in the course of disease. As laser therapy is not that much effective, pharmacological treatments may provide alternative strategy for DR. Both intra-vitreal corticosteroids and intra-vitreal anti- VEGF agents are widely used in clinical settings Diabetic vitrectomy increased life quality by improving vision. Early treatment for vitrectomy showed cost- effective intervention. Fenofibrate treated patients showed reduction in retinal laser therapy. The role of combination therapies is yet to be determined .Finally it was shown that DR can be treated in earlier stages.

The ideal medication for the treatment of DR is fast acting, long lasting and above all, safe. As the development of DR is a multi factorial process, involving inflammation and ischemia, future therapies, especially combination therapies, targeting different pathways may lead to more favourable outcomes.

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