WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 6, 46-61. Review Article ISSN 2277 – 7105

DIABETIC RETINOPATHY

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Article Received on
01 June 2014,

Revised on 26 June 2014,
Accepted on 21 July 2014

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ABSTRACT

Diabetic retinopathy is a major micro vascular complication of Diabetes mellitus that usually leads to blindness in working age adults throughout the world. Risk of Diabetic retinopathy increases in patients of type 1 and type 2 diabetes having hyperglycemia, blood pressure, oxidative stress, inflammation and micro/macrovascular complications. Diabetes effects all the 4 major types of retinal cells and interfere in their proper functioning. The purpose of this study was to understand the pathophysiological pathway behind the development of diabetic retinopathy and initial and long-term effects of insulin treatment on behavior of DR. Contents of this articles are based upon various studies and clinical trials conducted in various countries of the world showing the retinal cells structure, alteration of retinal cells in diabetes, pathophysiology of DR, blood–retinal barrier breakdown, Retinal micro vascular dysfunction and use of Insulin its effect and various other therapies. In addition this study also shows the relationship between the developments of cognitive impairment due to DR. finally, an overview of various drug therapies have also been provided. It showed that in addition to use of insulin to delay the worsening of DR, laser therapy, intravitreal anti-Vascular Endothelial Growth Factor treatment, steroidal injections and carbonic anhydrase inhibitors cause significant stabilization or even improvement from diabetic retinopathy. **Conclusion:** From this study, it can be concluded that now a days in young adults DR is a challenging disease to manage due the high prevalence of Diabetes mellitus. This review

demonstrates that with the current concepts and novel therapeutic approaches diabetic retinopathy can be manage. Regular screening examination and self-monitoring of blood glucose can reduce the extent of DR related visual impairment. Other new therapies are in pipeline, and forthcoming randomized clinical trials are required to study the effect of all these novel therapies.

KEY WORDS: Diabetic Retinopathy (DR), Diabetes Mellitus (DM).

INTRODUCTION

Diabetes mellitus has become a serious challenge for health care organization throughout the world due to its wide-ranging occurrence and economic burden. DR is a major micro vascular complication of Diabetes mellitus that usually leads to blindness in working age adults throughout the world (Muhammad shamsulola et al., 2012). The risk of vision loss according to World Health Organization is expected to be double till the year 2030, if the ratio of DM epidemic increases with current rate (Wild et al., 2004). According to International diabetes federation by year 2025, DM is expected to affect 380 million population (IDF-Atlas, 2006). A survey data showed that out of 10 diabetic patients 1 having diabetic retinopathy which can be control by keeping the glycemic values in normal range (Ju Yean Yang et al., 2013). Risk of Diabetic retinopathy increases in patients of type 1 and type 2 diabetes having hyperglycemia, blood pressure, oxidative stress, inflammation and micro/macro vascular complications (Daniel petrovic, 2014).

DR is a disease caused by damage of small blood vessels of retina due to high level of blood glucose in poorly controlled diabetic patients and may lead to increased retinal vascular permeability, retinal ischemia, proliferation of retinal vessels and vision loss (Q. Mohamed et al., 2007).All the patients suffering from type 1 diabetes develop this disease and ratio is above 60% in those having type 2 diabetes (R. Williams et al., 2004; R. Klein et al., 1998). This review translates the cell types and common treatments of diabetic retinopathy. Alteration in retinal cells takes place in this disease which leads to retinal inflammation and macular edema (Thomas W et al., 2002).

Studies

A study based on clinical data was performed in japan among 383 type 2 diabetic Japanese patients to check the progression and prevalence of diabetic retinopathy in males and females. Females displayed a considerably higher prevalence of proliferative DR as compared to male

(A. Kajiwara et al., 2014). Another study was conducted in a large European cohort Gutenberg Health Study (GHS), in which a population of pre diabetic patients were included to determine the association of DR with cardiovascular risk factors. There was found no association between diabetic retinopathy and cardiovascular risk factors such as dyslipidemia, chronic obstructive pulmonary disease, stroke, congestive heart failure, smoking, history of myocardial infarction, chronic kidney disease, coronary heart disease, obesity and peripheral artery disease (Julia Lamparter, 2014). 50% of patients with early onset of diabetes of any type between ages 10 to 25 years develop retinopathy with 10 to 12 years of diabetes history, and have a great need of regular eye screening, tight glycemic control and normal blood pressure for prevention of diabetic retinopathy (Ramachandran Rajalakshmi et al., 2014).

Retinal Cells

Diabetes effects all the 4 major types of retinal cells: 1) Endothelial cells and Pericytes, 2) glial cells, 3) neuronal cells, 4) microglial cells (Thomas W et al., 2002).Glial cells control metabolism of retina and regulate function of blood vessels and neurons that's why these cells can also be termed as support cells (Abbott NJ, 1992).The second class of cells contains neurons, which transmit nerve impulses to brain through optic nerve and nerve fibers of axons. Microglial class of cells involve tissue macrophages which are very sensitive to retinal homeostasis and become phagocytic as the homeostatic state of the retina changes (Broderick C et al., 2000).Neurons involves four types of cells such as ganglionic, amacrine, photoreceptors and bipolar cells which perform photo transduction and facilitate accurate vision (Gardner TW, & Aiello LP, 2000).

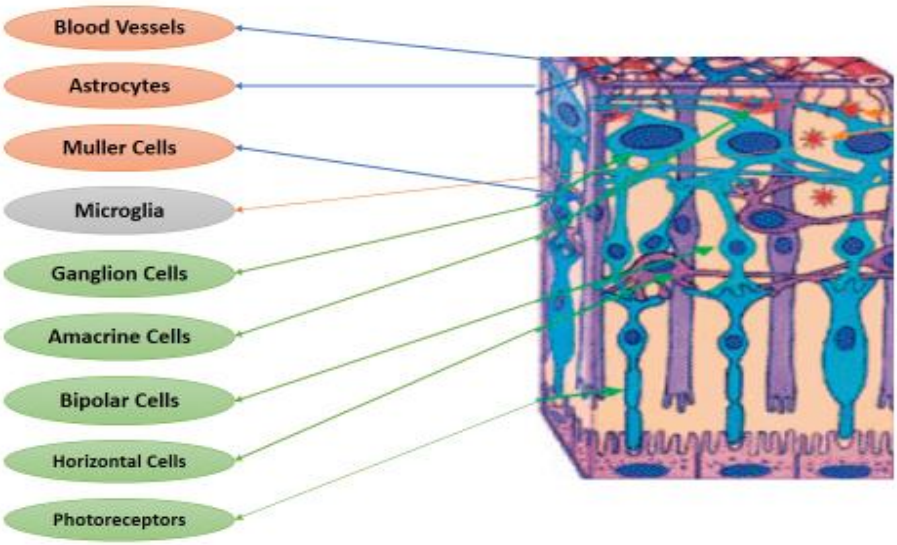

Fig 1. Schematic diagram retinal cell types: Microglia, macroglial cells (muller cells and astrocytes), vascular, neurons (bipolar cells, amacrine, photoreceptors and ganglion cells)

In diabetes their disturbance leads to diabetic retinopathy and vision loss. Smooth muscle cells of capillaries known as pericytes and endothelial cells are lining of blood vessels which by contraction and dilation regulate retinal blood flow and homeostatic functions by constituting blood–retinal barrier respectively. Astrocytes and Müller cells are the two basic types of macroglia which assimilate neuronal and vascular activity in the retina (Thomas W et al., 2002). For normal vision Accurate function and assimilation of all these cells are required, disruption of any of them may impair vision. The blood flow to retina auto regulate in response of any stimulus influence locally or systemically (Harris A et al., 1998), impaired metabolism of retina in diabetes disturb the function of auto regulation of retinal circulation (Sinclair SH et al., 1982).

Role of ROS in DR

In DR various biochemical changes takes place that disturb the functioning of retina by changing its microscopic structure. These biochemical changes occur when due to elevated serum glucose level, proper retinal metabolism can't take place and as a result retinal oxidative stress (ROS) formation takes place. These species cause up regulation of retinal vascular endothelial growth factor (VEGF), DNA, proteins, and lipids, and ultimately cause cell death. On other hand antioxidant defense mechanism also becomes impaired in DM, so ROS has a great contribution in not only DR development but also in its worsening and progression in case of diabetes Mellitus (Jose Javier et al., 2014), diabetic macular edema (DME) and proliferative diabetic retinopathy (M. I. lopez-galvez et al., 2014). Thickening or presence of hard exudates in retina within one disc diameter of the center of the macula is known as Diabetic macular edema (AnantPai et al., 2010; The Early Treatment of Diabetic Retinopathy Study Research Group, 1985; Klein et al., 1991, 1995; Neelakshi et al., 2009).Visual loss in most of the patients with DM is caused by Diabetic macular edema (Klein et al., 1984; moss et al., 1988). The occurrence of Diabetic retinopathy (DR), Proliferative DR (PDR) and vision threatening retinopathy was estimated globally and found to be 93Millions, 17M and 28M respectively (Bashira A Charles 2014). if any of the following three conditions is present then diabetic macular edema becomes significant macular edema: (1) in the center of the macula, retinal thickness is or within 500 micro meter, (2) in the center of the macula, hard exudates is or within 500 micro meter if associated with thickening of the adjacent retina, (3) in the center of the macula, zone or zones of retinal thickening of at least one disc diameter in size or of which is within one disc diameter (The Early Treatment of Diabetic Retinopathy Study Research Group, 1985).

Paradoxical effect of insulin therapy on DR

When intensive insulin therapy is given to patient of DM it provide short term worsening of DR at earlier stages but long term therapy leads to slow down the progression of DR (Jorge L. Jacot, & Aaron I. Vinik 2007). In this review the comparison of two studies were done, first study was a 10 year diabetes control and complication trial (DCCT) in which patients showed improvement in reduction of DR progression and macular edema (DCCT, 1995), not from the onset of insulin therapy but after 7 years of continuous treatment (DCCT, 1997). According to united kingdom prospective diabetes study (UKPDS) insulin have long term beneficial effects on DR in type 2 DM. first study showed reduction in progression of DR 27% in primary cohort and then 34-76% in DCCT in patients of type 1 DM, and 25% in type 2DM in UKPDS (UKPDS, 1999).

The pathophysiology behind the early worsening of DR due to intensive insulin therapy is still not clear but appearance of macular edema and exudates provide a link of breakdown of blood retinal barrier. Retinal vascular endothelial growth factor (VEGF) expression increases when insulin bind to HIF-1α, and VEGF promoter become activated and give rise to VEGF transcription through phosphatidylinositol 3-kinase (PI3K), N-terminal kinase and mitogen-activated protein kinase (MAPK) pathways. In DM increased VEGF causes breakdown of blood retinal barrier (Poulaki V et al., 2002; Saishin Y et al., 2003), as shown in figure 2. Endothelial cells that diturb to perform its proper function due to hyperglycemia and show a metabolic control by insulin therapy (Le Roith D et al., 2004). John F. Payne & Vin Tangpricha hypothesized that hypovitaminosis D cause worsening of DR, as diabetes cause hypovitaminosis D and tremendous effect of diabetes has seen on angiogenesis, control of blood pressure, insulin secretion, glucose tolerance and inflammation (John F. Payne, & Vin Tangpricha, 2014).

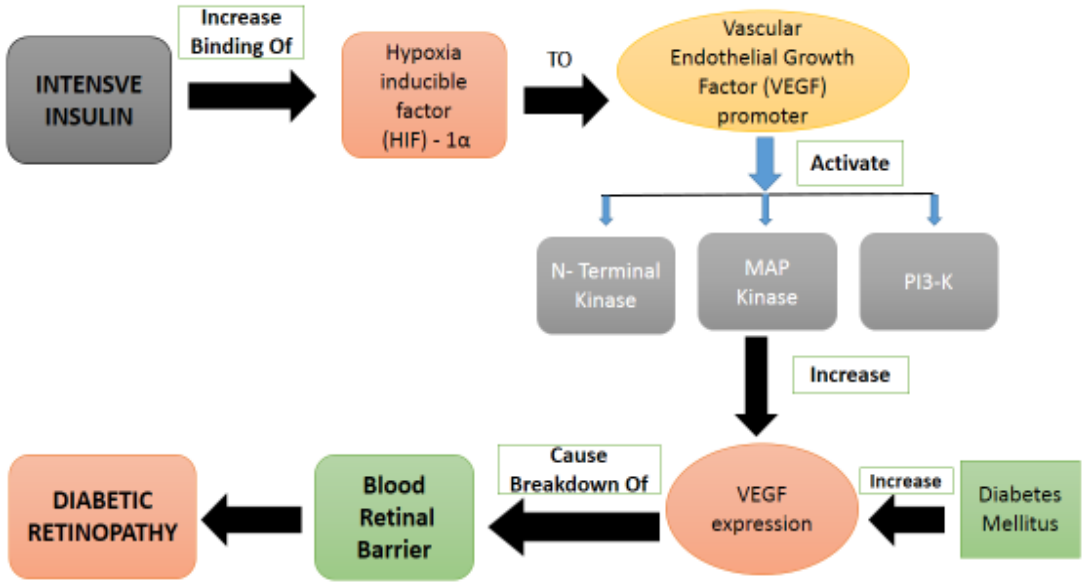

Fig 2. Early worsening of DR with intensive insulin treatment

DR and Cognitive impairment

Cognitive impairment and dementia is a recently identified complication of diabetes (Strachan MW et al., 1997; Cukierman T et al., 2005; Biessels GJ et al., 2006; Mariani E et al., 2007; Strachan MW et al., 2008; Strachan MW et al., 2009). Cognitive impairment is the existence of degree of cognitive dysfunction between dementia and normal aging (R. Crosby-Nwaobi et al., 2012). In diabetes 20-60% risk of cognitive impairment considerably increases (Cukierman T et al., 2005; Biessels GJ 1999; Luchsinger JA et al., 2007; Elias PK et al., 1997; Strachan MW et al 2003; Knopman D etal., 2001; Hassing LB et al., 2004; Leibson CL et al ., 1997; Peila R, et al., 2002; Ott A et al., 1999). Blood brain barrier is similar to blood retinal barrier and High blood glucose level cause micro vascular damage in that retinal barrier (Patton N et al., 2005). Patients who have retinopathy have increased risk of cognitive impairment (Lesage SR et al., 2009). Level of association between Cognitive impairment and DR is significantly greater for patients with diabetes. A review was conducted on the relationship between diabetic eyedisease and cognitive impairment in Type 2 diabetes to determine the level of association between diabetic retinopathy and cognitive impairment. 10 studies were included and 3 out of 10 studies showed a level of association between diabetic retinopathy and cognitive impairment. All these studies showed an increased risk of cognitive

impairment in patients with diabetic retinopathy, but none of the study showed the relationship of severity of DR and cognitive impairment (R. Crosby-Nwaobi et al., 2012).

Drug therapy to treat Diabetic Retinopathy

To treat patients with diabetic retinopathy, insulin therapy should be initiated in combination with periodic follow-up examinations and a thorough ophthalmologic evaluation for monitoring the progression of retinopathy for at least 18 to 24 months (Jorge L. Jacot and Aaron I. Vinik 2007). First step to control Diabetic Retinopathy is to manage the DM because persistent hyperglycemia is a major risk factor in development of DR. Tight glycemic control resulted by the HbA1c level not only reduces progression of DR but also its development (The Diabetes Control and ComplicationsTrial Research Group, 1993; UK Prospective Diabetes Study (UKPDS) Group, 1998). Management of blood pressure can also reduce diabetes induced retinal complications (Funatsu and Yamashita, 2003; Matthews et al., 2004; Sheth et al., 2006). Formation of Retinal hard exudates in patientswith retinopathy has also been reported by Hyperlipidemia, and some studies showed that lipid-lowering therapy may reduce hard exudates and microaneurisms (Shethet al., 2006; Lyons et al., 2004; Miljanovic et al., 2004; Chewet al., 1996; Klein et al., 1991).These treatments not only delay the development of DR but also slow the progression of retinal lesions into more severe forms.

Laser therapy

Laser photocoagulation therapy is the ordinary practice of managing PDR (The Diabetic Retinopathy Study Research Group, 1976, 1981, 1987), it reduces outer layers oxygen demand of the retina and helps to divert this adequate oxygen and nutrients to the inner retinal layers by changing the hemodynamics to the ischemic inner retina. This will reduce the vascularendothelial growth factor's (VEGF) hypoxia-mediated secretion and regression of neovascularization. But this laser treatment is not effective in some patients with PDR and DME and they continue to lose vision despite the prompt laser treatment (AnantPai et al., 2010). In some patients especially of diffuse CSME, the grid lasertreatment is somewhat less effective and more variable in outcome(Neelakshi et al., 2009).

Steroid injections

Various types of drugs through various drug delivery systems arebeing tried inDR patients. Which includes: intravitreal steroid injections, intravitrealadministration of anti-VEGF drugs, peribulbar steroid injections, and injection of sustained-release steroid andintravitreal implants. All these drugs are in different clinical trial levels (AnantPai et al., 2010). To treat

the pathogenesis of DR Forpatients with whonon responsive to laser therapy themost common second-line treatment is given, which includes intravitreal steroids and intravitreal anti-VEGFtherapy.Corticosteroids are alsouse in managing the DR, among them triamcinolone acetonide (TA) is more common(Silva et al., 2009). It cans be administered by various routes, containing intravitreal depotin jection, posterior subtenon injection, intravitreal implant and periocular injection. It's most common complication is that it raises intraocular pressure and form cataract, less common complications are retinal detachment and Endophthalmitis. It's been reported that Intravitreal triamcinolone reduce the risk of these adverse events. Some clinical trials show that for the treatment of PDR and macular edema the combination of laser photocoagulation with intravitreal TA showed improved visual acuity and decreased central macular thickness when compared with laser photocoagulationalone (Kanget al., 2006; Lam et al., 2007; Maia et al., 2009).

Anti-vascular endothelial growth factor therapy in DR

In the management of DR the most commonly studied anti-VEGF molecules are: ranibizumab, pegaptanib, bevacizumab and VEGFTrap-eye (Neelakshi et al., 2009; Jardeleza and Miller, 2009). Treatment with bevacizumabis most commonly use because it is less expensive, and an option for patient who are unable to undergo surgery or refuse surgery due to their general condition (Abdulla and Fazwi, 2009). It also uses to prevent or decrease PRP associated macular edema. A few days before the planned surgery, bevacizumab injection helps surgical removal of fibrovascular membranes, decrease intraoperative time, reduces intra-operative bleeding, prevents re-bleeding (Ishikawa et al., 2009; Yeoh et al., 2008; Chen and Park, 2006; Rizzo et al., 2008). After vitrectomy prolonged and recurrent vitreous hemorrhage is a common complication associated with vitrectomy for diabetic retinopathy with an incidence ranging from 12%to 63% (Abdulla and Fazwi, 2009; Novak et al., 1984; Yang et al., 2008). Use of intra-vitreal bevacizumab with or without supplementary endo photocoagulation at the end of surgery decreases the frequency of re-bleeding. Combination of intravitreally administered steroids and anti-VEGF drugs improve the therapeutic effects in DME patients who are unresponsive to laser therapy by improving visual acuity and reducing the macular thickness (Tsilimbaris et al., 2009).

Carbonic anhydrase to treat diabetic retinopathy

Families of enzymes known as Carbonic anhydrases (CAs) are responsible for the quick conversion of carbon dioxide tobicarbonate and protons. The carbonic anhydrase inhibitors

are used to lower intraocular pressure (B. Becker, 1954). CA inhibition reduces vascular leakage and macular edema caused by fluidretention in the retina due to vascular permeability (D.B. Pedersenetal., 2005; T.J. Wolfensberger 1999). Acetazolamide is given which inhibit carbonic anhydrase and decrease the rate of aqueous humor production. Various animal studies confirmed that fluid retention can be decrease by CA inhibitors acetazolamide (M.F. Marmor& T. Maack (1982) and benzolamide (M.F. Marmoretal 1980). DR cause Vasoconstriction which decreases blood flow, causes metabolicwaste accumulation and hypoxia. A large number of studies demonstrate that CA inhibitor Cause ocular vasodilation and improves retinal blood flow. Dorzolamide increase retinal vessel diameters on systemic administration. Hypoxia induce neovascularization and angiogenesis in DR (S.J. Isenberg et al., 1986). Oxygen tension elevation induced by CA inhibitor because due to increase in oxygen supply dorzolamide causes dilatation of the central retinal vessels and the duration of this dilatation mimics that cause rise in retinal oxygen tension (D.B. Pedersenetal., 2005). DR causes platelet aggregation which cause capillary occlusion and ischemia in the retina (A.M. Brooks et al., 1983). CA inhibitor Showed decreases the velocity of thrombin-stimulated platelets aggregation (W. Siffert et al., 1984; W. Siffert & G. Gros; 1984).

CONCLUSION

Diabetic retinopathy is a serious global public health problem that reduces the quality of life. In next 25 years throughout the world diabetic patients are predicted to become double who are at risk for developing vision loss from diabetes. In this review pathways involve in DR have been discussed, but the exact mechanism involve in progression is still uncertain. Retinal samples can't be taken from living humans that's why exact mechanism of DR can't be analyze. Further studies are required to better evaluate the effect of various drug therapies to manage diabetic retinopathy and blindness cause by DR. clinical trials have shown that Long term use of Insulin prevent the worsening of DR, and tight glycemic control delays its progression. For tight glycemic control accurate administration of insulin plays a pivotal role. If insulin is not properly administer its desired effect can't be achieved. It involves selection of correct insulin type, appropriate site to administer, knowledge of storage condition of insulin and formation of proper skin fold to administer it. Ophthalmologists and physicians both are performing their role to improve the vision affected with diabetes. Patients with DR have a great need of regular eye screening, tight glycemic control and normal blood pressure for prevention of diabetic retinopathy.

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