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Diabetic Retinopathy: An Overview

Nalini. M [*1], Veera Raghavulu[1]. B, Annapurna. A[1], Chandi Vishala. T[1]
A.U. College of Pharmaceutical Sciences, Andhra University, Vishakhapatnam, Andhra Pradesh, India.

Corresponding author: Nalini. M,
A.U. College of Pharmaceutical Sciences, Andhra University.
Vishakaptnam-530003, India

Abstract:- Diabetic retinopathy is a major cause of blindness in adults and diabetes is one of the reasons for retinal changes. These changes are mainly dependent on the duration of diabetes where all of type 1 diabetes patients are prone to retinopathy where as 60% of type 2 patients will develop retinopathy in developing countries including India. Though there are several molecular mechanisms causing diabetic retinopathy (DR) such as polyol pathway, protein kinase pathway, role of oxidative stress, inflammation and many more. But the exact mechanism by which diabetes causing diabetic retinopathy is not known yet. Although the treatment and development of new therapeutic strategies are less in India, it became necessary to work more on pharmacological mechanisms involved in diabetic retinopathy and therapeutic targets for the reducing the vision loss due to DR in countries like India. The aim of this paper is to introduce the pharmacological pathways that are involved in the development of a diabetic retinopathy namely increased expression several molecular factors such as vascular endothelial growth factor (VEGF), Intracellular adhesion molecule (ICAM), inflammation and free radicals are discussed in this paper. The recent advancements in molecular mechanisms, retinal cell survival and the new therapeutic targets for the treatment of diabetic retinopathy are discussed in this review.

Keywords:- *Diabetic Retinopathy (DR), Intra cellular adhesion molecule (ICAM-1), Vascular endothelium growth factor (VEGF), Tumor necrosis factor alpha (TNF), oxidative stress.*

I. INTRODUCTION

Diabetes is a major metabolic disorder where excess glucose levels in the blood are reported due to impaired glucose metabolism due to insulin deficiency or insulin resistance in body [1]. Due to hyperglycemia during the later stages of diabetes leads to retinal vascular changes causing diabetic retinopathy (DR) which finally leads to vision loss in adults of developing countries like India. Diabetic retinopathy was classified into non proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) characterized by the growth of new blood vessels (retinal neovascularisation). Early identification of the retinopathy and estimation of circulating biomarkers may reduce the risk of blindness due to diabetic retinopathy. The main risk factors responsible [2] for the progression of the DR is hyperglycemia, poor glycemic control, duration of diabetes. The prevalence of diabetic retinopathy is under reported in India when compared to other Asian countries. A cohort study conducted by **Ji-Hyun Kim** *et al* reported that the prevalence of diabetic retinopathy was 18% in rural Korea which was similar to other Asian countries [3] and the severity of diabetic retinopathy was increased with the duration of Diabetes mellitus, increased HbA1c levels in blood [4]. The prevalence of the disease was more in type 1 diabetes patients i.e., almost all the individuals with type1 diabetes and 60% of type2 individuals will develop diabetic retinopathy during first two decades of disease [5]. According to WHO reports, the prevalce of dr was as given below.The prevalence of diabetic retinopathy is almost 70% and prevalance of PDR was in 50% of type 1 diabetes patients >30 years [6]. The prevalence of DR in patients <30 years is 62% and PDR was 25% in typeI [7]. In typeII diabetes the prevalence of DR is 36% and PDR is 5% [7,8]. There are several pharmacological mechanisms responsible for reduced vision in diabetic individuals but there exact involvement of various mediators in disease progression and treatment strategies are still unknown. Therefore a number of trails are in progress for the new treatments strategies and pharmacological therapy for diabetic retinopathy.

II. MECHANISMS OF DIABETIC RETINOPATHY

Diabetes is the main culprit for major body complications like diabetic retinopathy with vascular structural and functional changes in the retina. Vascular changes causes ischemic condition in the retinal cells and altered adhesion of leukocytes [9]. Neovascularisation and increased vascular permeability are the key players in vision loss in diabetic retinopathy condition. The vascular endothelial growth factor (VEGF) and intracellular adhesion molecule (ICAM), inflammation and oxidative stress shown in fig 1, which is produced during pathogenesis of polyol pathway and protein kinase C pathway in retinal cells, are mainly responsible for the development of diabetic retinopathy [10].

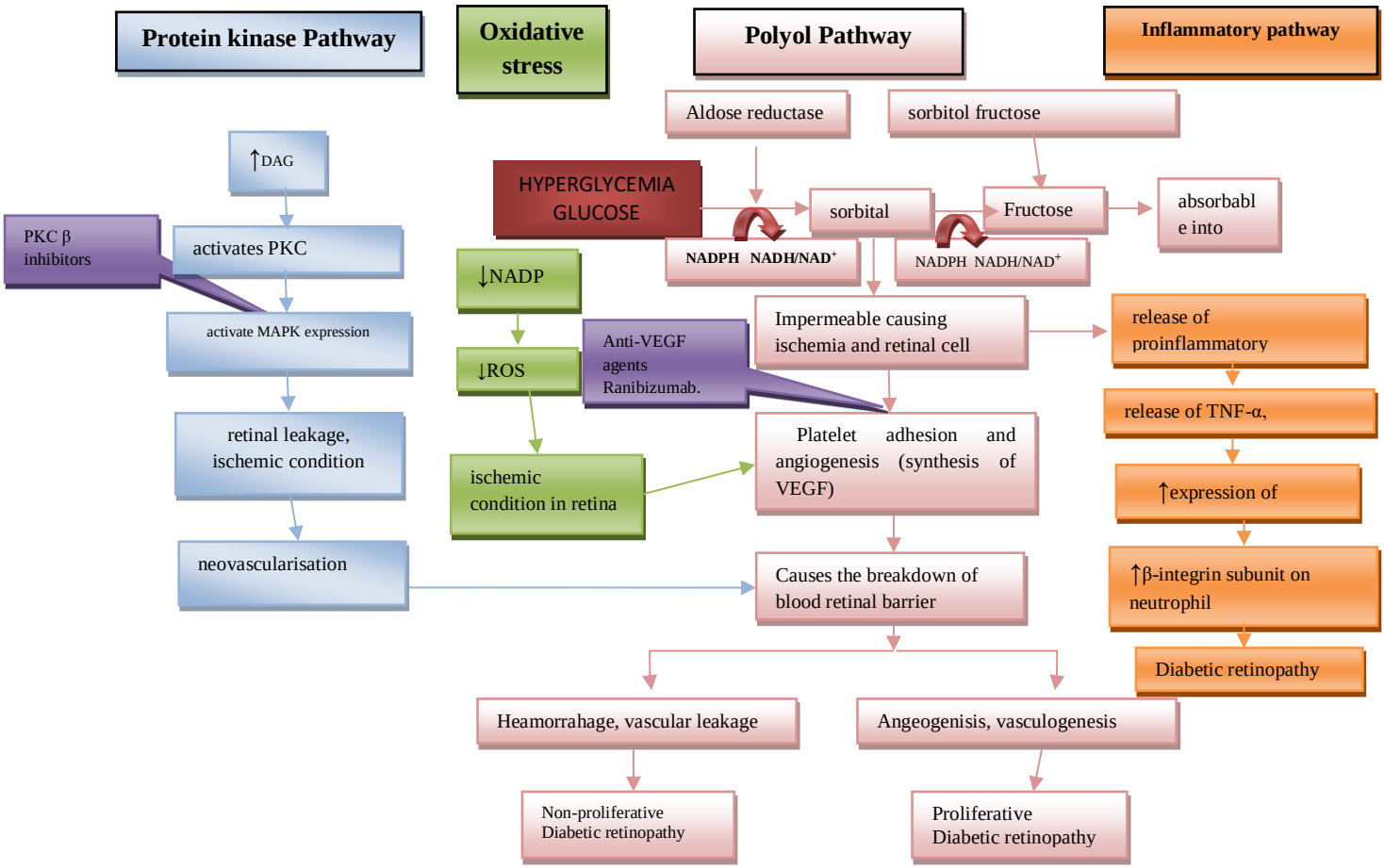

Fig. 1: Schematic representation of various possible mechanisms involved in the progression of diabetic retinopathy

A. Polyol Pathway

During hyperglycemic condition there is an increase in polyol pathway [11]where excess glucose is reduced to sorbitol with aldose reductase enzyme in which NADPH is a co-factor converted to NADH/NAD$^+$. Thus sorbitol is further converted to fructose by sorbital dehydrogenase and here NADPH acts as co-factor. In hyperglycemic condition increased polyol pathway flux was seen in tissues like kidneys, retina and in peripheral nerves [12].In this pathway the formed sorbitol is impermeable to the cell member causing damage to retinal cells including osmotic damage ie ischemia and cell death shown in fig 1. Sorbitol is an alcohol and hydrophilic nature and converted to fructose which was easily absorbable [13]. Due to ischemic condition adhesion of platelets was present during which neovascularisation begins. Then the retinal cells produce new cells from existing cells causing angiogenesis which finally cause the synthesis of vascular endothelial growth factor (VEGF) which aids in the formation of neovascularisation[12]. The Vascular endothelial growth factor which was produced during angiogenesis was one the therapeutic target for treatment of diabetic retinopathy where anti-VEGF agents will be used for treatment of DR. VEGF is an pleitropic nature with several receptors require for its actions such as proliferation, migration and tube formation required for angiogenic growth of new blood vessels. In mammals there are seven members of VEGF family they are VEGF A, VEGF B, VEGF C, VEGF D, VEGF E, VEGF F, VEGF G. In the deletion of any single allele of these variants block the angiogenic process [14]. The VEGF family show there action through binding to receptors they are VEGFR-1, VEGFR-2, VEGFR-3. VEGFR-1, VEGFR-2 is mainly for angiogensis and VEGFR-3 for hemopoiesis and lymphogenesis [9]. VEGF-2 levels are increased causing endothelial cell proliferation, migration and micro vascular permeability as in proliferative diabetic retinopathy (PDR). A study conducted by **Park HY** *et al* reported that inhibiting VEGF by using anti-VEGF antibody in rats have detrimental effects on apoptosis of neuronal cells in diabetic retinal cells [15]. Due to the complications in pan retinal photocoagulation which was used in the treatment of PDR, this brought an idea of anti-VEGF agents for diabetic retinopathy such as **Ranibizumab**, Bevacizumab, Aflibercept are generally used for the treatment of PDR [16], inhibiting VEGF may have detrimental effects on the apoptosis of neuronal cells in the inner layers of the diabetic retina.

B. Inflammation in Diabetic Retinopathy:

Inflammation is a part of the complex biological response of body tissues to harmful stimuli such as pathogens, damaged cells or irritants. This is a protective response that involves immune cells, blood vessels and molecular mediators. Neovascularisation and angiogeninesis suggest a possible role of inflammation in pathology of diabetic

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retinopathy. Inflammation involves the activation of several proinflammatory mediators such as cytokines and chemokines. TNF-α which is a cytokine is a primary mediator in inflammation is produced in the retinal cells activates the expression of intercellular adhesion molecule (ICAM-1), VEGF isoforms [17]. Hence the levels of TNF-α, ICAM-1, VEGF are `increased in the vitreous and serum samples of diabetic retinopathy patients. An in-vitro study stated that TNF-α treated cells increased the gene expression of ICAM-1 through increase VEGF expression [18]. Leukocytes with help of ICAM- 1 lead to leukocyte adhesion to the vascular cells of retina causing leukostasis which is a characteristic feature in inflammation. This leukocyte activation and increase in ICAM-1 leads to the progression of diabetic retinopathy. In turn this activation of leukocytes causes disruption of blood retinal barrier causing angiogenesis. Leukocytes lead to production of VEGF, a proinflammatory mediator which promote the release of ICAM-1 and VCAM [17]. Now-a day's anti-VEGF drugs are being used for the treatment of diabetic retinopathy, as VEGF promote the expression of ICAM-1 leads to leukocyte adhesion and release of other chemokines and cytokines which enhance the inflammatory response in retinal vascular cells. Muller cells in retina produce large amounts of VEGF, in diabetic mice inhibition of this muller cells caused a reduced expression of TNF-α, ICAM-1, VCAM and leukosatsis [19]. Mice deficient with gene encoding ICAM-1 and CD 18 showed less leukocyte adhesion when diabetes was induced in the same mice, this condition showed a less damage to retinal endothelial cells and development of diabetic retinopathy was delayed [19,20]. C-reactive protein measures a general risk of inflammation in the body. Hence, a study conducted by **Abdul El-Asrar AM** on diabetic rats showed an significant increase in the expression of TWEAK(Tumor necrosis factor-like weak inducer of apoptosis), Fn14 (Fibroblast growth factor-inducible molecule 14) in the vitreous samples of diabetic rats which are responsible for inflammation followed by neovascularisation in the development of PDR. So, this **TWEAK/Fn 14** pathways might be a novel targets for the treatment of diabetic retinopathy.

C. Protein kinase pathway:

Vascular changes in the eyes of diabetic patients arise from one of the pathomechanism i.e, hyperglycemia induced activation of protein kinase c (PKC) [11]. Protein kinase C (PKC) molecule is a part of a serine/threonine kinase family that catalyzes phosphorylation of several proteins in endothelial permeability,[22] PKC pathway was enhanced by increased DAG diaceyl glycerol due to high glucose levels, which activates PKC isoforms causing vascular dysfunctions and pathogenesis of diabetic retinopathy. Increased PKC activity in diabetic retinopahty leads to changes in endothelial permeability, blood flow causing angiogenic growth factors, this formation leads to retinal leakage, ischemia and neovascularisation in retina cells.PKC activation leads to mitogen-activated protein kinase (MAPK) activation shown in fig 1 and increase gene expression of various stress related genes in retina. PKC contributes to signaling component for VEGF as binding of VEGF to its receptors i.e., VEGF-R2 [23] hydrolysis of phosphoinositol that causes the release of DAG in turn activates PKC pathway. PKC activation is responsible for the pathology in DR [24]. There are several isoforms of protein kinase C which regulates several body functions among which PKC β is responsible for vascular damage of retina. Therefore PKC β inhibitors such as Ruboxistaurin are used as a novel therapeutic target for diabetic retinopathy [25].

D. Oxidative stress

Retina consists of high oxygen uptake and more glucose oxidation capacity which resembles that retinal cells are easily susceptible to oxidative stress [26]. The main agent responsible for oxidative stress is production of ROS reactive oxygen species [11] .Which was produced during various cellular process like electron transport chain, NADH oxidase , cytochrome P450. The generated ROS [26] has to be regenerated by cellular antioxidants in normal healthy conditions. During diabetic retinopathy condition excess ROS [27] is produced which leads to pathological condition. In the ploy ol pathway where NADPH was used as a cofactor for the conversion of sorbitol to fructose where NADPH is converted to $NADH/NAD^+$. This NADPH is required for generating cellular antioxidants. Hence in diabetic condition due to increased polyol pathway there is reduced availability of NADPH for cellular antioxidants causing increased oxidative stress shown in fig 1 in retinal cells [28]. Due to inadequate NADPH there is greater ischemic condition of retina leads to neovascularisation and release of VEGF. Superoxide radicals a reactive oxygen species (ROS) is produced in increased oxidative stress [29]. Greater ROS increase the release of other oxidative intermediates and advanced glycation end products which lead to increased release of VEGF. Both ischemia and increased oxidation lead to increase lipid peroxides which are angiogenic themselves [30]. Animal studies has shown that hyperglycemic conditions for 6months have produced retinal damage causing retinopathy with increased lipid peroxide levels, but even good glycemic control for 7 months did not reverse retinopathy condition [31]. Superoxide radical, reactive oxygen species (ROS) is produced in increased oxidative stress. A clinical study conducted in diabetic retinopathy [32] patients showed a significant co-relation between serum lipid peroxidation and duration of diabetes [30, 33]. One study has reported that free radicals formed in diabetic retinopathy palys a key role in the development of diabetic retinopathy [33, 34].

III. CONCLUSION

The purpose of this review is to provide a brief understanding of various molecular mechanisms involved in the pathogenesis of diabetic retinopathy. Initially people should have a good control on hyperglycemia in order to reduce the risk of diabetes induced vision loss. Diabetic retinopathy was detected by retinal scan and scatter laser photocoagulation and the same method was used to know the progression of the disease. At the advanced stage vtirectomy is done to restore the vision loss. Once diabetic retinopathy develops there is no cure for the disease unless reducing the vision loss, the therapeutic agents such as various drugs mentioned in the review are preferred at the proliferative stage of diabetic retinopathy. The main culprits for the development of diabetic retinopathy can be any of the molecular mechanisms mentioned in this paper. Hence, novel

drugs acting in various pathways for the treatment of diabetic retinopathy are also mentioned in this review which can be available for treatment and reducing the progression of diabetic retinopathy.

CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

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