Diabetes & Metabolic Syndrome: Clinical Research & Reviews 9 (2015) 51–54

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Diabetic retinopathy – Biomolecules and multiple pathophysiology

Haseeb Ahsan

Department of Biochemistry, Faculty of Dentistry, Jamia Millia Islamia, Okhla, New Delhi 110025, India

ARTICLE INFO

Keywords:
Diabetic retinopathy
Retina
Glutamate
AGE
ROS
PKC

ABSTRACT

One of the major complications in patients with diabetes is diabetic retinopathy (DR), a leading cause of blindness worldwide. It causes visual impairment and finally blindness, a result of long-term accumulated damage to the small blood vessels in the retina. It takes several years before any clinical symptoms of retinopathy appear in diabetic patients. Consequently, glycemic control, blood pressure and lipid-lowering therapy have all shown benefits in reducing the incidence and progression of DR.

A number of hyperglycemia-induced metabolic stresses have been implicated in the pathophysiology of DR. The microvasculature of the retina responds to hyperglycemia through a number of biochemical changes, including the activation of protein kinase C (PKC), increased advanced glycation end-products (AGEs) formation, polyol pathway and oxidative stress. There is an accumulating body of evidence indicating that inflammation and neurodegeneration play an important role in the pathogenesis of DR.

Contents

1. Introduction

In complex diseases like diabetes mellitus the causative agents include various serum factors like glucose, insulin, advanced glycation end products (AGEs), lipids and lipoproteins, leucocytes and their regulators, growth factors and cytokines such as vascular endothelial growth factor (VEGF), tumor necrosis factor α (TNFα), insulin like growth factor (IGF) and connective tissue growth factor, intracellular mediators such as mitogen activated protein kinases (MAPK), nuclear factor κB (NFκB), polyADP ribose polymerase (PARP), phosphatidylinositol 3 kinase (PI3K), protein kinase C (PKC) and aldose reductase, vasocative substances such as nitric oxide (NO) and endothelin, oxygen free radicals such as superoxide anion radical ($O_2^{\cdot -}$) and various antioxidant enzymes such as catalase, superoxide dismutase (SOD), etc. [1–3].

Diabetic retinopathy (DR) is one of the most common complications of diabetes affecting millions of adults worldwide, in which the retina of the eye becomes progressively damaged, leading to vision loss and blindness as a result of long-term accumulated damage to the small blood vessels in the retina (Fig. 1). It takes several years before any clinical symptoms of retinopathy appear in diabetic patients [3]. Consequently, glycemic control, blood pressure and lipid-lowering therapy have all shown benefits in reducing the incidence and progression of DR [3–5]. DR is a multifactorial progressive disease of the retina where the pathogenesis of the disease is extremely complex involving many different cells, molecules, and factors [6].

In the last few decades a number of hyperglycemia-induced metabolic stresses (e.g., the activation of protein kinase C (PKC), poly ADP-ribose polymerase (PARP), increased flux through the hexosamine pathway, and the accumulation of polyols and advanced glycation end-products (AGEs) have been implicated in the pathophysiology of diabetes via the increased production of

Abbreviations: DR, diabetic retinopathy; ROS, reactive oxygen species; PKC, protein kinase C; AGEs, advanced glycation end products; Glu, glutamate; WHO, World Health Organization; CNS, central nervous system.

E-mail address: drhahsan@gmail.com.

http://dx.doi.org/10.1016/j.dsx.2014.09.011
1871-4021/

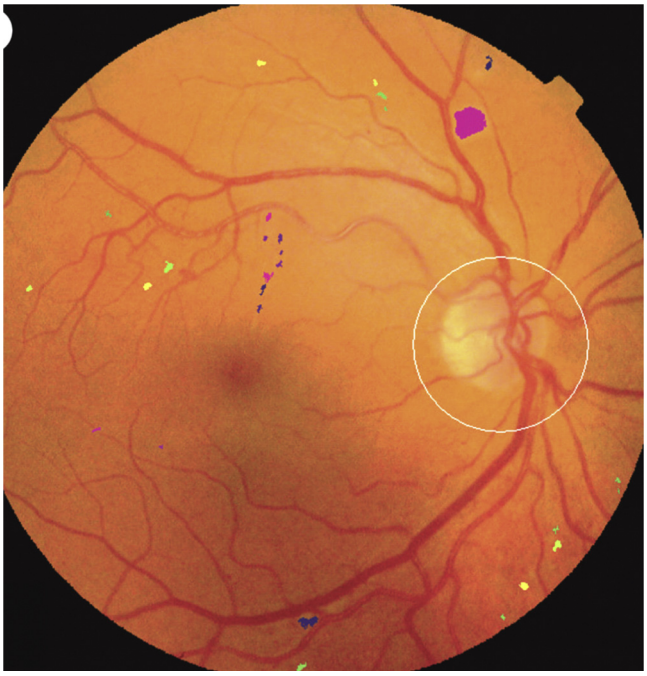

Fig. 1. Image of a patient with diabetes classified as having cotton-wool spots, exudates and hemorrhages caused by diabetic retinopathy (adapted and reprinted from [35]).

reactive oxygen species (ROS) [7]. Oxidative stress initiates four major molecular events implicated in the pathogenesis of diabetic complications such as increased polyol synthesis, formation of advanced glycation end products (AGEs), activation of protein kinase C (PKC) and enhanced flux through the hexoasmine pathway [8]. Other processes associated with DR include the acceleration of inflammatory responses, the upregulation of the renin–angiotensin system (RAS), and the dysregulation of growth factors [3,9].

According to World Health Organization (WHO), the prevalence of DR is expected to increase, and the number of people at risk of vision loss is predicted to double by the year 2030 with the increasing rate of diabetes epidemic [10]. Approximately, 346 million people have diabetes worldwide, about 10% of diabetic people have severe visual impairment, and 2% become blind [11] (Fig. 2). The Diabetes Control and Complications Trial [12] and the UK Prospective Diabetes Study [13] established that hyperglycemia is

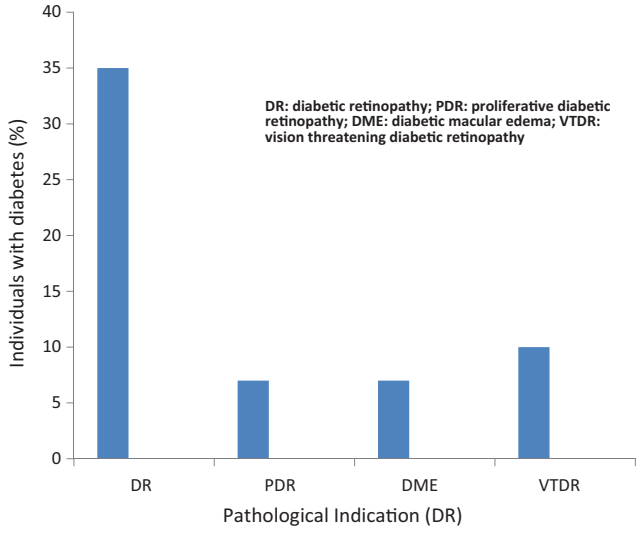

Fig. 2. Global prevalence of diabetic retinopathy.

the initiating cause of retinal damage. The underlying biochemical mechanisms associated with hyperglycemia and identified in diabetic retinas include activation of PKC, increased formation of advanced glycation end products (AGEs), polyol formation, increased hexosamine fluxes, activation of the renin–angiotensin system (RAS) and production of excess ROS. Numerous studies suggested that increase in fluxes through these pathways may lead to a cascade of events, such as promotion of apoptosis, inflammation and angiogenesis, which may, in turn, induce damage to retina, leading to DR.

The retina is a simple evagination of the brain, located at the back of the eye and representing the central nervous system (CNS). The function of retina is to encode light signals into electrical signals corresponding to relative luminance and detection of differential motion and edges. Vertebrate retina can be classified into either vascular, which have blood vessels entering into it or avascular, that receive their nutrient supply directly for the choroidal circulation.

The retina consists of a number of cells, and normal vision depends on intact cell-cell communication among them. Diabetes manifests in damaging all of the major retinal cells including endothelial, Muller, ganglion, and pigment epithelial cells. Diabetes damages all the major retinal cells of the retina, vascular cells (endothelial cells and pericytes) [14,15], neurons (photoreceptors, bipolar, horizontal, amacrine and ganglions), [16–20], glia (Müller cells and astrocytes) [17,18,21], microglia [22] and pigment epithelial cells [23].

But, before damage, these cells are activated, which modifies the mediators, such as growth factors, vasoactive agents, coagulation factors and adhesion molecules, resulting in increased blood flow, increased capillary permeability, proliferation of the extracellular matrix and thickening of basal membranes, altered cell turnover (apoptosis, proliferation, hypertrophy), procoagulant and proaggregant patterns and, finally, in angiogenesis and tissue remodeling. The mechanisms of diabetes-induced damage to retinal cells correlate with excessive circulating levels of glucose, lipids, hormones, amino acids and inflammatory molecules.

Diabetes induces abnormal levels of metabolites such as glucose, lipids, amino acids, hormones, and nutrients, and several factors have been found to activate those retinal cells before the damage. A number of studies suggest a high plasma level of homocysteine in diabetic patients [24,25] and increased level of branched chain amino acids in diabetic retina may damage neuronal cell death in DR [26]. In addition, dysregulated level of taurine and its transporter in diabetic retina has been shown to be implicated in pathophysiology of DR [27,28]. Moreover, the role of nutrients such as alpha lipoic acid, folic acid, vitamin C, vitamin E, and minerals has also gained interest in the pathophysiology of DR [29].

During the past few decades, hyperglycemia has been considered as the major contributor and inducer in the progression of the disease. However, a number of studies suggest that excess plasma glucose may not account for the range of cellular and functional changes in the progression of DR [30–32]. Several studies indicate that even intensive therapy to control blood glucose has some long-term effects on the risk of DR [4,5]. The increased systemic, vitreal, and retinal levels of those metabolites and factors in diabetic patients and in various animal models of the disease have been shown to induce several unrelated and interrelated biochemical pathways and molecules implicated in the progression of the disease [3] (Table 1).

Diabetic retinopathy is widely considered to be a neurovascular disease. Early in the disease progression of diabetes, the major cells in the neuronal component of the retina consist of retinal ganglion cells and glial cells, both of which have been found to be compromised. A number of retinal function tests also indicated a functional deficit in diabetic retina, which further supports