Anatomical and Functional Change of the Macula after Vitrectomy of Tractional Diabetic Macular Edema

Thesis

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List of Abbreviations

Abb.	Full term
AGEs	*Advanced Glycation End Products*
ANG-2	*Angiopoietin – 2*
BRB	*Blood Retinal Barrier*
CFT	*Central Foveal Thickness*
CME	*Cystoid Macular Edema*
CPM	*Cuts Per Minutes*
CSME	*Clinically Significant Macular Edema*
DCCT	*Diabetes Control and Complications Trial*
DIRECT	*Diabetic Retinopathy Candesartan*
DME	*Diabetic Macular Edema*
DN	*Diabetic Nephropathy*
DR	*Diabetic Retinopathy*
ELM	*External Limiting Membrane*
ERM	*Epiretinal Membrane*
ETDRS	*Early Treatment Diabetic Retinopathy Study*
FFA	*Fundus Fluorescence Angiography*
HbA1c	*Hemoglobin A1c*
HDL	*High-Density Lipoprotein*
ICAM-1	*Intracellular Adhesion Molecules - 1*
IDF	*International Diabetes Federation*
IL	*Interleukin*
ILM	*Internal Limiting Membrane*
LogMAR	*Logarithm of the Minimum Angle of Resolution*
ME	*Macular Edema*
MENA	*Middle East and North Africa*

List of Abbreviations (Cont...)

Abb.	Full term
MMPs	*Matrix Metalloproteinases*
PDGF	*Platelet-Derived Growth Factor*
PDR	*Proliferative Diabetic Retinopathy*
PKC	*Protein Kinase C*
PPV	*Pars Plana Vitrectomy*
RAGE	*Receptor for Advanced Glycation End Products*
RD	*Retinal Detachment*
RPE	*Retinal Pigmented Epithelium*
SD-OCT	*Spectral Domain Optical Coherence Tomography*
TGF	*Tissue Growth Factor*
TNF-α	*Tumor Necrosis Factor-Alpha*
TRD	*Tractional Retinal Detachment*
TRE	*Tractional Retinal Elevation*
TRS	*Tractional Retinoschisis*
UKPDS	*United Kingdom Prospective Diabetes Study*
VEGF	*Vascular Endothelial Growth Factor*
VMA	*Vitreo-Macular Adhesions*
VMT	*Vitreo-Macular Traction*

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INTRODUCTION

With increasing prevalence of diabetes mellitus and increasing life span of persons with diabetes, diabetic retinopathy (DR) is set to be the leading global cause of vision loss in many countries ***(Cheung et al., 2010).***

The International Diabetes Federation (IDF) estimates that 32.8 million adults are affected by diabetes in the Middle East and North Africa (MENA) region, and by 2030, this number will double to 59.9 million ***(Whiting et al., 2011).***

Retinopathy is a common and specific microvascular complication of diabetes which affects 17–54% of people with diabetes aged 49–60 years and remains the leading cause of preventable blindness in working-aged people ***(Macky et al., 2011), (Cheung et al., 2010).***

DME is more prevalent in type 2 diabetes and is the primary cause of moderate visual loss for diabetic patients. Apart from the effects on vision, the presence of DR and DME is a marker of concomitant diabetes complications in other organ systems ***(Simó and Hernández, 2009).***

The exact pathogenesis of DME is still unclear. But increased vasopermeability occurs as a result of breakdown of the blood retinal barrier (BRB) due to many factors: altered glial cells, loss of pericytes, endothelial cell death, leukostasis in the retinal vasculature, poor function of the tight junctions in

the retinal vasculature, upregulation of the expression of vascular endothelial growth factor (VEGF) and protein kinase C (PKC), and altered vitreo-retinal interface with a thickened taut, posterior hyaloid with persistent vitreo-macular traction (VMT) ***(Bhagat et al., 2009).***

Vitreomacular traction (VMT) syndrome is a potentially visually significant disorder of the vitreoretinal interface characterized by an incomplete posterior vitreous detachment with the persistently adherent vitreous exerting tractional pull on the macula and resulting in morphologic alterations and consequent decline of visual function ***(Peter and Sanket, 2015).***

Spectral Domain Optical Coherence Tomography (SD-OCT) allows non-invasive visualization and imaging of vitreomacular interface and is an important tool in the diagnosis and management of VMT syndrome ***(Bottós et al., 2012).***

Pars plana vitrectomy (PPV) is the routine treatment for symptomatic VMT, performed with the aim of releasing the residual vitreomacular adhesions (VMA) in order to restore normal central retinal architecture. PPV is an effective surgical therapy for VMT resulting in a gain of two or more Snellen lines of visual acuity in 45% to 100% of eyes associated with reduction of mean foveal thickness. ***(Jackson et al., 2013).***

Aim of the Work

To evalute the efficacy of pars plana vitrectomy with or without internal limiting membrane (ILM) peeling in tractional diadetic macular edema, as regards the visual acuity and OCT changes of the macula.

Chapter 1

EPIDEMIOLOGY

The International Diabetes Federation (IDF) listed Egypt among the world top 10 countries in the number of patients with diabetes. It is expected that the number of patients with diabetes in the Middle East and North Africa (MENA) region to grow by 96% from year 2013 to 2035 or from 34.6 million to 67.9 million. In Egypt, the prevalence of diabetes is around 15.56% among adults between 20 and 79 years of age ***(Jain and Saraf, 2010), (Whiting et al., 2011).***

Egypt has the highest number of people living with diabetes in the Middle East and North African region at ~7.8 million, which accounts to ~22% of people living with diabetes in this region. Globally, Egypt is the 8th country in the world for the number of people living with diabetes.

Epiretinal membrane (ERM) was found in 27% to 34% in eyes with DME ***(Gandorfer et al., 2005), (Sakimoto et al., 2008),*** while vitreomacular traction was seen in 4 to 25% of DME cases ***(Ghazi et al., 2007), (Ophir et al., 2010).***

Risk Factors for DR and DME

Hyperglycemia

One of the most important predictive factors for DR and DME is the level of glycemic control. Two landmark clinical trials, the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) provided strong evidence that tighter control of glycemia (HbA1c 7 %) reduces the risk of development and progression of DR in both type 1 and type 2 diabetes ***(Mohamed et al., 2007).***

The DCCT showed that intensive glycemic control reduced the incidence of retinopathy by 76 % and progression from early to advanced retinopathy by 54 %. Each percent reduction in HbA1c (e.g., from 9 % to 8 %) lowers the risk of retinopathy by 30–40 % and the effect is long-lasting ("metabolic memory") ***(White et al., 2008).***

Hypertension

Hypertension is considered as an important modifiable risk factor for DR ***(Mohamed et al., 2007).*** Each 10-mmHg increase in systolic blood pressure is associated with an approximately 10 % excess risk of early DR and a 15 % excess risk of PDR or DME ***(Gallego et al., 2008).***

Patients with hypertension and tight blood pressure control had a 37 % reduction in the risk of microvascular disease, a 34 % reduction in the rate of progression of retinopathy, and a 47 % reduction in the deterioration of visual acuity in people with type 2 diabetes ***(Mohamed et al., 2007).*** However, these benefits are not sustainable without ongoing and long term maintenance of blood pressure control ***(Holman et al., 2008).***

In the multicenter Diabetic Retinopathy Candesartan Trials (DIRECT), candesartan, an angiotensin II receptor blocker, a specific blood pressure lowering agent, found to reduce the incidence of retinopathy by two or more steps in severity on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale by 18 % or by three or more steps by 35 % in type 1 diabetes, and increased regression of retinopathy by 34 % in type 2 diabetes ***(Mitchell and Wong, 2008), (Chaturvedi et al., 2008).***

Dyslipidemia

Dyslipidemia could have a role in the severeity of DR especially with increasing triglycerides and inversely associated with High-density lipoprotein (HDL) in type 1 diabetes ***(Benarous et al., 2011).***

Pregnancy

DR and DME can progress rapidly during pregnancy ***(Vestgaard et al., 2010)*** especially in type 1 diabetes. However, this is thought to be usually a transient effect. DR has a high regression rate in the end of pregnancy or in the postpartum period ***(Rasmussen et al., 2010).***

Renal impairment

In 2014, Kim and his colleagues found that patients with diabetic nephropathy (DN) show a more rapid progression to PDR. After adjustment for other risk factors, patients with albuminuria showed an increased risk of progression to PDR. Albuminuria is one of the indicators of generalized microvascular disease in diabetic patients; therefore, it is a risk factor for both DR and DN ***(Kim et al., 2014).***

More careful ophthalmologic follow-up is recommended when albuminuria develops in patients with DR. More recently, a statistically significant association was identified between DN and DR. It was also shown that renal impairment preceded and produced the eye involvement, which was proportional to the renal dysfunction ***(Kotlarsky et al., 2014).***

Chapter 2

PATHOGENESIS

The vascular system of the retina is complex, and the retinal neural tissue is protected from potentially harmful molecules in circulation, and excess fluid by the blood-retinal barrier (BRB) ***(Klaassen et al., 2013).*** Hyperglycemia causes damage to blood vessels and the BRB, and results in increased vascular permeability ***(Bhagat et al., 2009).*** This causes fluid and molecules to leak into the retina, with extracellular accumulation of fluid and the deposition of macromolecules, leading to the development of retinopathy.

Diabetic maculopathy is a condition that can result from retinopathy and consists of damage to the macula, the part of the retina which provides us with our central vision. A common form of damage is from diabetic macular edema (DME) in which fluid builds up on the macula ***(Haller et al., 2010).*** DME is characterized by vascular leakage, tissue edema and the deposition of hard exudates in the central retina ***(Klaassen et al., 2013).***

Hyperglycemia

Hyperglycemia causes overproduction of reactive oxygen species in the mitochondria, which leads to oxidative stress and tissue damage through a number of major mechanisms (Figure 1). These mechanisms include: Increased

flux of glucose and other sugars through the protein Kinase C pathway (which triggers phosphorylation of tight junction-associated proteins to induce BRB breakdown), polyol pathway, Increased intracellular formation of advanced glycation end products (AGEs) and increased expression of the receptor for AGEs, Activation of the protein kinase C isoforms, and overactivity of the hexosamine pathway (Figure 2).

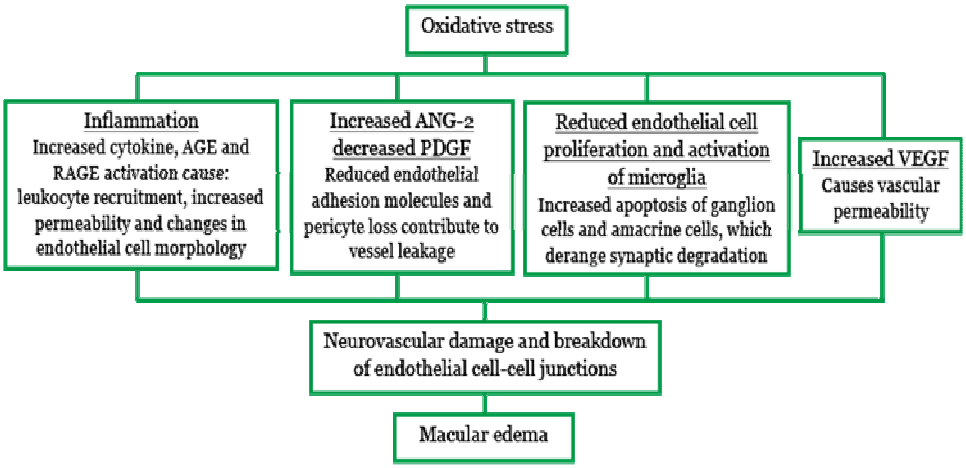

Figure (1): Hyperglycemia leads to oxidative stress and impacts distinct pathways ***(Giacco and Brownlee, 2010).***

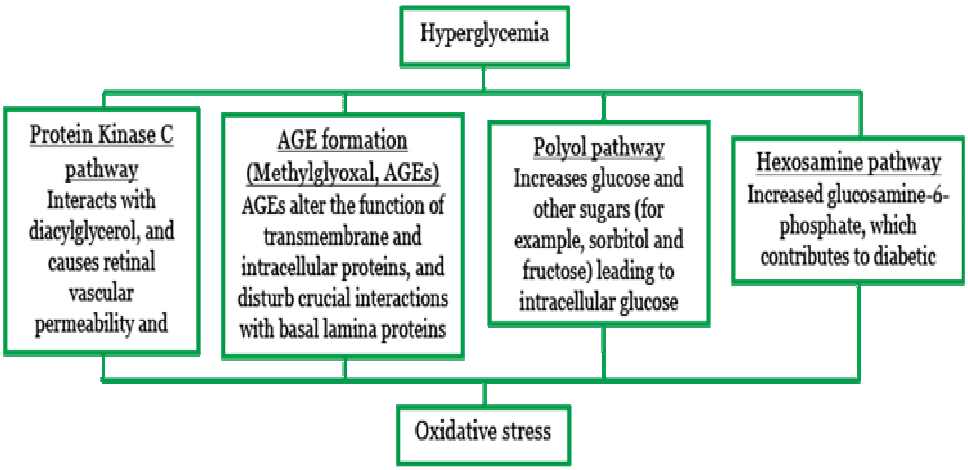

Figure (2): Oxidative stress leads to BRB breakdown and macular edema ***(Amoaku, 2015).***