Recent Trends in Treatment

of

Diabetic Retinopathy

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SUMMARY

Diabetic retinopathy (DR) remains one of the leading causes of visual morbidity. Worldwide, there are approximately 194 million people with diabetes, and this number is likely to increase to 334 million by 2025. DR is divided into two major forms: non-proliferative and proliferative.

After 20 years with the disease, 60% of type-2 diabetics and virtually 100% of type-1 diabetics will manifest some form of retinopathy. Generally, the prevalence of retinopathy at diagnosis of type-1 diabetes is reportedly low, between 0% and 3% while a higher proportion of those with newly diagnosed type-2 diabetes have evidence of DR 6.7–30.2%.

Eyes with obvious foveal involvement by edema or lipid are categorized as "severe DME". Eyes with edema and/or lipid relatively distant from the macula are graded as "mild DME", "Moderate DME" was used to identify cases in which retinal thickening and/or lipid are close to the fovea.

The exact mechanism by which diabetes causes retinopathy remains unclear, but several theories have been postulated to explain the typical course and history of the

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LIST OF ABBREVIATIONS

Abcg2	ATP-Binding Cassette Transporter g2
ACE	Angiotensin Converting Enzyme
AGEs	Advanced Glycation End Products
ARMD	Age Related Macular Degeneration
BCVA	Best Corrected Visual Acuity
BRB	Blood Retinal Barrier
BRVO	Branch Retinal Vein Occlusion
CMT	Central Macular Thickness
CRT	Creatine Transporter
CRVO	Central Retinal Vein Occlusion
CSME	Clinically Siginificant Macular Edema
DAG	Diacylglycerol
DCCT	Diabetic Control and Complication Trial
DM	Diabetes Mellitus
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
ENT2	Equilibrative Nucleoside Transporter 2
ERMs	Epi-Retinal Membranes
ETDRS	Early Treatment Diabetic Retinopathy Study
Fab	Antigen-Binding Fragment
FAZ	Foveal Avascular Zone
FDA	Food and Drug Administration
FFA	Fundus Fluorescine Angiography
GAPDH	Glyceraldehyde-3-Aldehyde Dehydrogenase
GLUT1	Glucose Transporter 1

HMG-CoA	Hydroxy-Methl-Glutaryl Co-enzyme A
IGF-1	Insulin-like Growth Factor-1
ILM	Iinternal Limiting Membrane
IOP	Intra-Ocular Pressure
IRMA	Intra-Retinal Microvascular Abnormalities
IVTA	Intra-Vitreal Triamcinolone acetonide
JAM	Junction Adhesion Molecule
LAT1	L-type Amino Acidtransporter 1
MAGI	Membrane- Associated Guanylate Kinases with Inverted domain structures
MCT1	Monocarboxylate Transporter 1
mdr1a	Multidrug Resistance 1a
mf-ERG	Multi-focal Electroretinogram
MUPP1	Multi-Pdz Protein-1
MVL	Moderate Visual Loss
NADH	Nicotinamide Adenine Dinucleotide
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
Nd:YAG	Neodymium: Yttrium-Aluminium-Garnet
NOS	Nitrous Oxide Synthase
NPDR	Nonproliferative Diabetic Retinopathy
NV	Neovacularization
Oatp1a4	Organic Anion Transporter Polypeptide 1a4
OCT	Optical Coherence Tomography
PDR	Proliferative Diabetic Retinopathy
PGF	Placental Growth Factor
PKC	Protein Kinase C

PPV	Pars Plana Vitrectomy
PRP	Pan-Retinal Photocoagulation
PSC	Posterior Sub-Capsular
RBX	Ruboxistaurin mesylate
ROS	Reactive Oxygen Species
RPE	Retinal Pigment Epithelium
RTA	Retinal Thickness Analyzer
RVO	Retinal Vein Occlusion
SDM	Sub-threshold Diode Micro-pulse
SLT	Scanning Laser Tomography
TauT	Taurine Transporter
TGF-ß	Transforming Growth Factor ß
UKPDS	United Kingdom Prospective Diabetes Study
VEGF	Vascular Endothelial Growth Factor
VPF	Vascular Permeability Factor
WESDR	Wisconsin Epidimiologic Study of Diabetic Retinopathy
WESDR	Wisconsin Epidimiologic Study of Diabetic Retinopathy
YLF	Yttrium-Lithium-Flouride
ZO	Zonula Occludens

INTRODUCTION

Diabetic retinopathy is an important cause of visual morbidity. It damages retinal blood vessels, resulting in the breakdown of the blood-retinal barrier and increased vascular permeability ***(Williams et al., 2004).***

Diabetic retinopathy is the most common cause of legal blindness in individuals between the ages of 20 and 65 years. It is subdivided into non-proliferative and proliferative diabetic retinopathy. Non-proliferative diabetic retinopathy is graded as mild, moderate, or severe depending on the number of microaneurysms, intraretinal heamorrhage, venous beading, intraretinal microvascular abnormalities (IRMAs) and cotton-wall spots. Proliferative diabetic retinopathy is characterized by epiretinal outgrowth of new vessels and finally fibrous membrane formation ***(Ulbig & Hoops, 2000)***.

The prevalence increases with the duration of diabetes, and nearly all persons with type 1 diabetes and more than 60% of those with type 2 have some retinopathy after 20 years ***(Quresh et al., 2007).***

Retinal hypoxia is the natural consequence of retinal vascular dysfunction associated with diabetic eye disease. In response to local hypoxia, affected tissues in the retina and elsewhere upregulate the production of vascular endothelial growth factor (VEGF). VEGF is a potent angiogenic stimulus, and it also induces vascular permeability up to 50,000 times more potent than that of histamine. This will result in breakdown of the blood-retina barrier and accumulation of extracellular fluid with the subsequent development of macular edema ***(Ferrara & Gerber, 2003).***

Fundus Fluorescein angiography (FFA) is generally used in diagnosis and treatment planning. The method is useful in detecting early alterations of the blood-retinal barrier, capillary closure, and microaneurysm formation ***(Cunha-Vaz, 2000).***

Optical coherence tomography (OCT) is a non contact, non invasive imaging that obtains high resolution cross sectional imaging of the retina and has been shown to be effective in documenting various pathologies of the posterior segment, it is capable of quantifying the macular thickening in diabetic macular edema, it even detect thickness in absence of any abnormality on slit-lamp examination ***(Rivellese et al., 2000)***.

Laser treatment of diabetic retinopathy is still the gold standard of treatment for focal and diffuse diabetic macular edema and proliferative diabetic retinopathy. When properly treated, the 5-year risk of blindness is reduced by 90% in patients with proliferative diabetic retinopathy and the risk of visual loss from macular edema is reduced by 50% ***(Lang, 2007).***

Intravitreal triamcinolone acetonide (IVTA) has been applied in exponentially increasing frequency for various intraocular neovascular diseases, including diabetic macular edema, proliferating diabetic retinopathy, neovascular glaucoma due to proliferative diabetic retinopathy ***(Jonas J, 2007).***

Intravitreal Bevacizumab *(Avastin®)* injections may have a beneficial effect on macular thickness and visual acuity (VA), independent of the type of macular edema that is present. Therefore, in the future this new treatment modality could complement focal/grid laser photocoagulation in DME. ***(Arevalo & Garcia-Amaris, 2009).***

Newer therapeutic options are directed at the causative mechanisms of diabetic retinopathy. Experimental and clinical evidence suggests that pharmacological compounds like somatostatin analogues and protein kinase C (PKC) inhibitors may be effective in the treatment of diabetic retinopathy ***(Lang, 2007).***

Somatostatin analogues remain the only nondestructive therapeutic alternative to patients with proliferative diabetic retinopathy who have failed to respond to panretinal photocoagulation ***(Boehm B, 2007).***

Surgery for diabetic retinopathy addresses late secondary complications of a primary microvascular disease. The functional outcome of surgery depends on the degree of retinal ischemia and may be disappointing even in technically and anatomically successfully operated eyes ***(Horst Helbig, 2007).***