Updates on management of Proliferative diabetic retinopathy

Essay

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By

Mahmoud Ahmed Mahmoud
M.B.B.CH

Under supervision of

Prof.Dr.Hoda Mohamed Saber Naeim
Professor of ophthalmology
Faculty of medicine
Ain shams university

Dr.Reham Fawzy El-Shinnawy
Lecturer of ophthalmology
Faculty of medicine
Ain Shams University

Faculty of medicine
Ain Shams university
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List of abbreviations

AAO	American academy of Ophthalmology
ACE	Angiotensin Converting Enzyme
ACEi	Angiotensin-converting Enzyme Inhibitor
AGE	Advanced Glycation End Product
AGEs	Advanced Glycation End Products
ANG II	Angiotensin II
AR	Aldose Reductase
AT1R	Angiotensin type 1 receptor
BFGF	Basic Fibroblast Growth Factor
BP	Blood Pressure
BRB	Blood Retinal Barrier
CME	Cystoid Macular Edema
COX-2	Cyclooxygenase-2
CSME	Clinically Significant Macular Edema
CTGF	Connective Tissue Growth Factor
DCCT	Diabetic Control &Complication Trial
DIRECT	Diabetic Retinopathy Candesartan Trials
DM	Diabetes mellitus
DME	Diabetic Macular edema
DR	Diabetic retinopathy

DRS	Diabetic Retinopathy Study
eNOS	Endothelial nitric oxide synthase
ETDRS	Early Treatment Diabetic Retinopathy Study
ERG	Electroretinogram
EUCLID	Eurodiab Controlled Trial of Lisinopril in Insulin-dependent Diabetes
FA	Fluorescein Angiography
FGF	Fibroblast Growth Factor
GH	Growth Hormone
Hex	Hard exudates
H/Ma	Hemorrage&/or Microaneurysm
HGF	Hepatocyte Growth Factor
HIF-1α	Hypoxia Induced Factor-1 α
HRC	High-risk characteristics
HRT	Heidelberg Retina Tomograph
ICAM-1	Intracellular Adhesion Molecule-1
IGF	Insulin-like Growth Factor
IL-6	Interleukin-6
iNOS	Inducible nitric oxide synthase
IOP	Intraocular Pressure
IRMA	Intaretinal microvascular abnormalities
IVB	intravitreally injected bevacizumab
IVTA	Intravitreal Triamcinolone acetonide

Ma	Microaneurism
MAPK	Mitogen-activated protein kinase
ME	Macular Edema
NADH	Nicotinamide Adenine Dinucleotide
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NO	Nitric Oxide
NPDR	Non-proliferative Diabetic retinopathy
NVD	Neovascularisation of the disc
NVE	Neovascularisation elsewhere
NVG	Neovascular Glucoma
OCT	Optical Coherence Tomograpy
PAF	Platelet Activating Factor
PEDF	Pigment Epithelial-derived Factor
PDGF	Platelet-derived Growth Factor
PDR	Proliferative Diabetic Retinopathy
PGF	Placental Growth Factor
PKC	Protein Kinase C
PPAR- γ	Peroxisome Proliferator-activated Receptor- **γ**
PRP	Panretinal photocoagulation
PVD	Posterior Vitreal Detachment
RAGE	Receptor for advanced glycation end products
RAS	Renine-angiotensin system
RBX	Ruboxistaurin
RCT	Randomized Controlled Trial

ROS	Reactive Oxygen Species
RPE	Retinal Pigment Epithelium
RTA	Retinal thickness analyzer
SDF-1	Stromal cell-derived factor-1
siRNA	Small interfering RNA
STZ	Streptozotocin
TA	Triamcinolone acetonide
T1DM	Type-1 DM
T2DM	Type-2 DM
TGF	Transforming Growth Factor
TGF-b	Transforming Growth Factor-beta
TNF- α	Tumor necrosis factor-*alpha*
TRD	Tractional Retinal Detachment
UKPDS	United Kingdom Prospective Diabetic Study
VA	Visual Acuity
VB	Venous beading
VCAM-1	Vascular Cell Adhesion Molecule-1
VEGF	Vascular Endothelial Growth Factor
VEGFRs	Vascular Endothelial Growth Factor Receptors
ZO-1	Zonula-Occludin-1
VVOs	Vesiculo-vacuolar Organells
WESDR	Wisconsin Epidemiological Study of DR

List of tables

List of diagrams

List of figures

INTRODUCTION

Diabetes mellitus (DM) affects 2.8% of population worldwide. Diabetic retinopathy (DR) is a specific micro-vascular complication of diabetes. DR is the leading cause of blindness in working - aged persons. The prevalence increases with the duration of diabetes, and nearly all persons with type I diabetes (T1DM) and more than 60% of those with type II (T2DM) have some retinopathy after 20 years **(Quresh. et al.,2007).**

Vision loss from diabetes is due to a number of factors including hemorrhage from new and poorly formed blood vessels, retinal detachment due to contraction of formed fibrous tissue and neovascular glaucoma. Diabetic macular edema (DME) is now the principle cause of vision loss in DM and involves leakage from a disturbed blood- retinal barrier (BRB). **(Yam and Kwok, 2007)** .

DR is essentially a clinical diagnosis. Slit lamp biomicroscopy, dilated fundus evaluation with a direct and indirect ophthalmoscope or contact/noncontact slit lamp biomicroscopic examination are essential in the diagnosis of DR. However, several ancillary investigations are required to aid the diagnosis,

plan and execute the treatment and to document the lesions for research purposes. Optical coherence tomography (OCT) and Stereoscopic fundus photographs may be required for research purposes and are especially useful for the assessment of DME. **(Singh et al., 2008)**

Strict metabolic and blood pressure control can lower the risk of DR and reduces disease progression.Laser photocoagulation and vitrectomy are effective in preventing severe vision loss in DR, particularly in the most advanced stages of the disease **(Yam and Kwok,2007).**

Recently there are new therapeutic approaches for the treatment of DR, the newer therapeutic options are directed at the causative mechanisms of DR,as angiotensin II (ang II) possibly participated directly and / or indirectly in th occurrence and development of DR via the upregulation the expression of vascular endothelial growth factor (VEGF). The experimental and clinical evidence suggest that these therapeutics as angiotensin – coverting enzyme inhibitors (ACEi) and angiotensin type1 receptor (AT1R) antagonists could improve DR to some degree and protect the retina **(Kurihara et al., 2008).**

Other pharmacological therapies are being developed .The latter target underlying biochemical mechanisms that cause DR through involvement of oxidative stress, the angiogenesis pathway, and the glycation and sorbitol pathway. These treatments aim to prevent diabetes-induced damage to the retinal microvasculature. **(Bhavsar , 2006).**

Chronic overproduction of growth hormone (GH) and insulin-like growth factor-1(IGF-1) play an important role in the pathogenesis of DR, so compounds like somatostatin analogues (e.g.octreotide) and protein kinase C (PKC) inhibitors may be effective in the treatment of DR and DME . **(Lang,2007)** .

Intravitreal injection of a slow release steroid, triamcinolone acetomide (IVTA),which suppresses inflammation,reduce extravasasion from leaking blood vessels and inhibits fibrovascular proliferation,has emerged as an another therapy for DME refractory to conventional laser photocoagulation. **(Cunningham et al.,2008)** .

Anti- VEGF drugs, administrated by repeated intravitreal injection offer great promise in managing proliferative DR (PDR) and DME. Bevacizumab (Avastin) is the most widely used anti-VEGF **(Averyl et al.,2006) .**

AIM OF THE WORK

To review the recent trends in the diagnosis and treatment of proliferative diabetic retinopathy

PATHOGENESIS OF DIABETIC RETINOPATHY AND DIABETIC MACULAR EDEMA.

BIOCHEMICAL BASIS FOR DR:

DM causes similar microvascular abnormalities in the retinal vasculature, renal glomeruli, and vasa vasorum. In the early stages of diabetes, chronic hyperglycemia results in blood flow alterations and increased vascular permeability. This is characterized by decreased activity of vasodilators such as nitric oxide (NO) and coexisting increased activity of vasoconstrictors such as (ANG II) and endothelin-1 with the release of vasopermeability augmenting cytokines such as VEGF. Resultant extracellular matrix abnormalities, both qualitative and quantitative, contribute to irreversible increases in vascular permeability **(Paul et al., 2008)**.

Microvascular cell loss occurs due to programmed cell death, the overproduction of extracellular matrix proteins and the deposition of periodic acid-Schiff-positive proteins induced by growth factors such as Transforming growth factor-b (TGF-b), all of which subsequently lead to progressive capillary occlusion. Hyperglycemia decreases the production of endothelial and