بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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Subthreshold micropulse yellow (577nm) laser versus intravitreal Ranibizumab in treatment of center involving diabetic macular oedema

THESIS
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List of abbreviations

BCVA	Best corrected visual acuity
BRB	Blood retinal barrier
CAMs	Cell adhesion molecules
CFT	Central foveal thickness
CI	Confidence interval
CMT	Central macular thickness
CMV	Central macular volume
CSME	Clinically significant macular oedema
CST	Central subfield thicknesss
CW	Continuous wave
DC	Duty cycle
DM	Diabetis mellitus
DME	Diabetic macular oedema
DR	Diabetic retinopathy
DRCR	Diabetic retinopathy clinical research network
DRS	Diabetic retinopathy study
EPM	Endpoint management
ETDRS	Early treatment diabetic retinopathy study
FAF	Fundus auto-fluorescence
FAZ	Foveal avascular zone
FcRn	Neonatal Fc receptor
FFA	Fundus fluorescein angiography
FT	Foveal thickness
HD-SDM	High density subthreshold diode micropulse
HSP	Heat shock proteins
ICAM	Intracellular adhesion molecules
IOP	Intraocular pressure
IVI	Intravitreal injection
MAPK	Mitogen activating protein kinase
mETDRS	Modified early treatment diabetic retinopathy study
mfERG	Multifocal electroretinogram

MPL	Micropulse laser
ND-SDM	Normal density subthreshold diode micropulse
NPDR	Non-proliferative diabetic retinopathy
NVAMD	Neovascular age related macular degeneration
OCT	Optical coherence tomography
PASCAL	Pattern Scan Laser
PEDF	Pigment epithelium derived growth factor
PDR	Proliferative diabetic retinopathy
PKC	Protein kinase C
PLGF	Placental growth factor
PPV	Pars plana vitrectomy
PRP	Pan retinal photocoagulation
RCTs	Randomized controlled trials
ROS	Reactive oxygen species
RPE	Retinal pigment epithelium
SD OCT	Spectral domain optical coherence tomography
SDM	Subthreshold diode micropulse
SRT	Selective retinal therapy
STMPL	Subthreshold micropulse laser
TGF-β	Transforming growth factor beta
VE	Vascular endothelial
VEGF	Vascular endothelium growth factor
VEGFRs	Vascular endothelial growth factor receptors
VVOs	Vesiculo-vacuolar organelles
ZO	Zonula occludin

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Introduction

The management of diabetic macular oedema (DME) has substantially changed over the years due to the advancement in pharmacotherapy with intravitreal injections (IVI) of anti-vascular endothelial growth factor (VEGF). However, the traditional laser treatment proposed by the Early Treatment Diabetic Retinopathy Study (ETDRS) is still being used for its efficacy, low cost and easy processing.

Despite the improvements and the satisfactory results of laser photocoagulation, adverse events such as central scotoma, loss of central vision, decreased color vision, preretinal and subretinal fibrosis and choroidal neovascularization can still occur, mostly caused by permanent destruction of the photoreceptors and the progressive enlargement of the laser scars, consequent to the visible burn endpoint of conventional threshold laser photocoagulation[1-2-3-4].

Results of the diabetic retinopathy clinical research (DRCR) network protocol I trial showed that intravitreal Ranibizumab (a humanized monoclonal antibody fragment which competitively inhibits VEGF in the extracellular space), with prompt or deferred laser was more effective compared with prompt laser alone for the treatment of DME involving the central macula after one year follow up, and that the vision gains were maintained through 5 years follow up with little additional treatment needed after 3 years [5-6].

Several other studies have been conducted to investigate the efficacy and safety of Intravitreal Ranibizumab in treatment of DME including the READ-2 study, the RESOLVE study, the

RESTORE study and the RISE and RIDE studies which showed that ranibizumab is effective in improving best corrected visual acuity (BCVA) and is well tolerated in DME[7-8-9-10].

Although Ranibizumab was demonstrated to be effective, a major concern, is that DME will return as the effect of the intravitreal drug lessens, necessitating repetitive long term injections. Another concern is the financial burden of repeated intravitral injections of ranibizumab. That led to the emergence of new modalities of laser treatment for management of diabetic retinopathy (DR), including selective retinal therapy (SRT) and subthreshold micropulse laser (STMPL) in which the modification of laser parameters and using selective laser wave lengths can produce less destructive and more therapeutic effect.

The state of the art of STMPL has been shown to be effective in the treatment of DME in terms of BCVA, central macular thickness (CMT), and macular sensitivity[11-12-13-14]. STMPL has also been suggested to have anti-inflammatory effects reducing the number of hyper-reflective spots (sign of activated microglia cells in the retina), microaneurysms, disorganization of the inner retinal layers extension, and the area of cysts[15]. Also, several prospective randomized trials have reported equal improvement in BCVA and retinal thickness between STMPL and conventional ETDRS laser photocoagulation in DME[16-17-18-19-20].

Diabetic macular oedema

DR is a leading cause of vision-loss globally. Of an estimated 285 million people with diabetes mellitus worldwide, approximately one third have signs of DR and of these, a further one third of DR is vision-threatening DR, including DME. DME is responsible for most of the visual loss experienced by patients with diabetes[21].

Pathophysiology of DME:

DME results from abnormal leakage of fluid and macromolecules, such as lipoproteins, from retinal capillaries (i.e. the inner blood retinal barrier (BRB) as shown in figure 1) into the extravascular space. This is followed by an influx of water into the extravascular space due to increased oncotic pressure[22], as shown in figure (2).

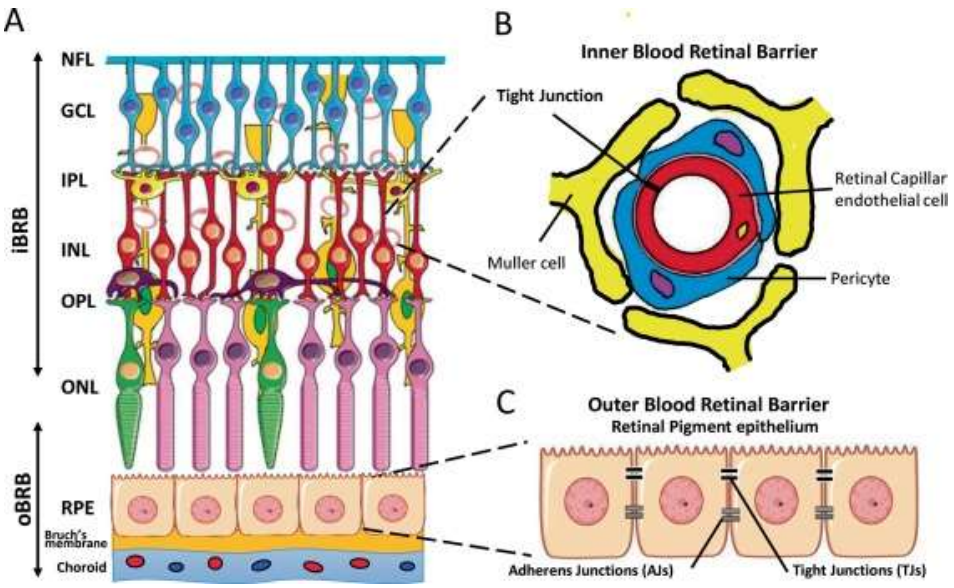

Fig.(1). Blood retinal barrier. (A) Schematic representation of the retinal layers with inner BRB and outer BRB. (B) Inner BRB. (C) Outer BRB[23].

The retinal pigment epithelium (RPE) normally acts as a barrier to fluid flow from the choriocapillaris to the retina and also actively pumps fluid out of the retina (i.e. the outer BRB as shown in figure 1). Thus, abnormalities in the RPE may contribute to DME allowing increased fluid access from the choriocapillaries or decreasing the normal efflux of fluid from the retina[22].

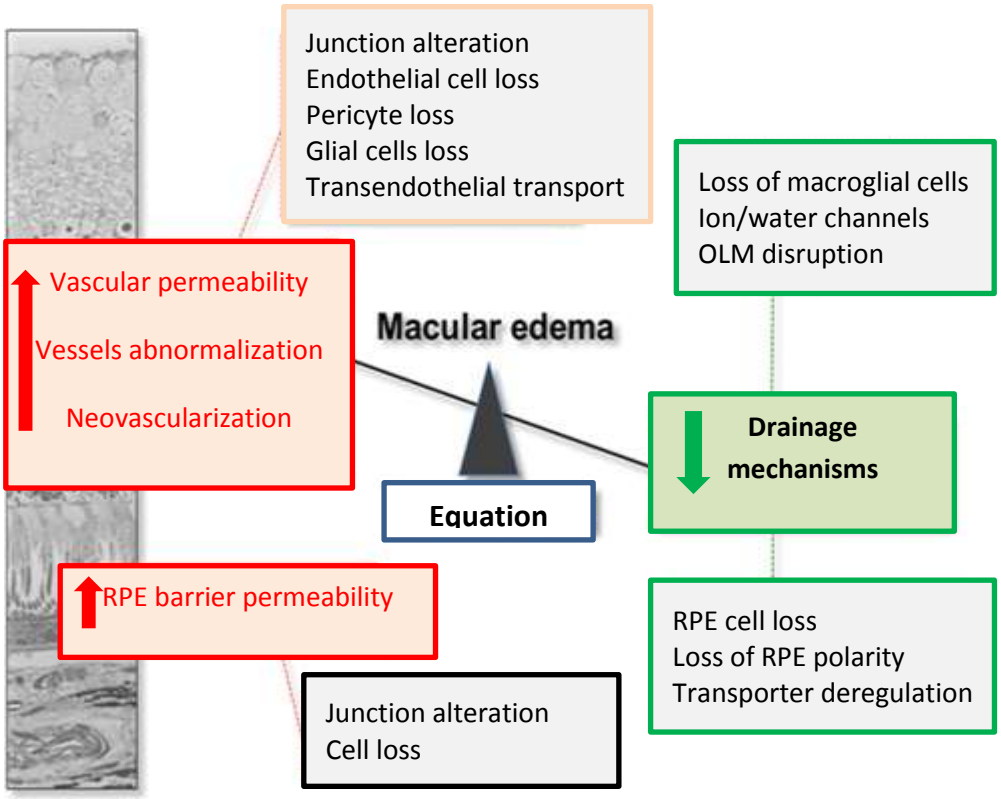

Fig.(2). Pathophysiological mechanisms leading to macular edema. Macular oedema results from an imbalance between fluid entry and fluid exit, leading to intraretinal or subretinal fluid accumulation, driven by Starling equation[22].

Hyperglycemia has been considered as the main cause of the onset and progression of DME and DR[24] as shown in figure (3). However, hyperglycemia does not fully explain the wide range of functional and cellular changes that appear over the course of DR.

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