Ain Shams University
Faculty of Medicine
Ophthalmology Department

Tomographic Assessment of Some Neural Elements Affection in Type I Diabetic Patients

Thesis Submitted In partial fulfillment of MSc degree in Ophthalmology

By

Mohamed Elsayed Elarabi Gharieb
MB.B.CH Faculty of Medicine, Zagazig University

Supervised by

Prof.Dr. Ossama Abd El-Monem Raslan
Professor of Ophthalmology
Faculty of Medicine – Ain Shams University

Dr. Wael Adel Gomaa
Lecturer of Ophthalmology
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
Cairo
2018


بسم الله الرحمن الرحيم
قَالوُاسُبحَانَك لاَعِلمَ لنَا إلا مَاعَلمتَناَ
إنكَ أَنتَ العَلِيمُ الحَكِيمُ
صدق الله العظيم
(سورة البقرة – الآية ٣٢)

First of all, I would like to thank Allah for helping and guiding me throughout my study and whole my life.

I would like to express my sincere appreciation to my supervisors. First to start with ***Prof.Dr. Ossama Abd El-Monem Raslan***, Professor of Ophthalmology, Ain-Shams University, who has been of utmost supreme guidance and supervision with overwhelming kind care and encouragement.

I would like to express my greatest gratitude to ***Dr. Wael Adel Gomaa***, Lecturer of Ophthalmology, Ain Shams University, who has performed his greatest effort and helped me from the beginning and throughout the practical part of the study.

Out of my supervisors, I am really indebted to ***Dr. Hesham Mohamed Gharieb***, Lecturer of Ophthalmology, Ain-Shams University, who had much helped me during my study in imaging OCT many deepest thanks for his extreme support.

I would like to thank all patients who accepted to be a part of this study for their helpful contribution.

At last but not at least, I would like to record my continuing debt and warmest gratitude from all of my heart to all my family members and my friends and thank them all for supporting me through the study period.

CONTENTS

List of Tables

List of Figures

List of Abbreviations

ADA	American Diabetes Association
AGEs	Advanced glycation end-products
ANOVA	Analysis of variance
BBB	Blood brain barrier
BCVA	Best corrected visual acuity
BRB	Blood retinal barrier
BUN	Blood urea nitrogen
CST	Center subfield thickness
D	Diopter
d.f.	Degree of freedom
DAG	Diacylglycerol
DBP	Diastolic blood pressure
DCCT	Diabetes Control and Complication Trial
DM	Diabetes Mellitus
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRT	Diffuse retinal thickening
ECM	Extracellular matrix
ELM	External limiting membrane
ERM	Epiretinal membrane
ETDRS	Early Treatment Diabetic Retinopathy Study
F	Fisher's Ratio
FA	Fluorescein angiography
FFA	Fundus Fluorescein Angiography
GCL	Ganglion cell layer
HbA1c	Glycosylated haemoglobin
HS	Highly significant
i-BRB	Inner blood retinal barrier
ICAM-1	Intercellular adhesion molecule-1
ILM	Internal limiting membrane
InfInLt	Inferior Inner Left
InfInRt	Inferior Inner Right
InfOutLt	Inferior Outer Left
InfOutRt	Inferior Outer Right
INL	Inner nuclear layer

IOP	Intraocular pressure
IOP	Intra ocular pressure
IPL	Inner plexiform layer
IRMA	Intraretinal microvascular abnormalities
IS/OS	Junction between the inner and outer photoreceptor segments
IS/OS PRL	Inner and outer segments of the photoreceptor layer
LGN	Lateral geniculate nucleus
Lt	Left
mm	Millimeter
mmHg	Millimeters of mercury
MS	Mean Square
N	Total number of subjects
NasInLt	Nasal Inner Left
NasInRt	Nasal Inner Right
NasOutLt	Nasal Outer left
NasOutRt	Nasal Outer Right
NFL	Nerve fiber layer
NO	Nitric oxide
No.	Number
NPDR	Non-proliferative diabetic retinopathy
NS	Non- Significant
OCT	Optical coherence tomography
ONL	Outer nuclear layer
OPL	Outer plexiform layer
OS-RPE	Outer segment of retinal pigmented epithelium junction
PDR	Proliferative diabetic retinopathy
PGF	Placental growth factor
PKC	Protein kinase C
PVD	Posterior vitreous detachment
RAGE	Receptors of advanced glycation end-products
RBCs	Red blood cells
RGCs	Retinal ganglion cells
ROS	Reactive oxidative species
RPE	Retinal Pigmented Epithelium
RT	Retinal thickness
Rt	Right

S	Significant
SBP	Systolic blood pressure
SD	Standard deviation
SD-OCT	Spectral-domain optical coherence tomography
SE	Standard Error
SPANOVA	Split plot analysis of variance
SPSS	Statistical Package for the Social Sciences
SS	Type III Sum of Squares
STDR	Sight-threatening diabetic retinopathy
SupInLt	Superior Inner Left
SupInRt	Superior Inner Right
SupOutLt	Superior Outer left
SupOutRt	Superior Outer Right
TempInLt	Temporal Inner Left
TempInRt	Temporal Inner Right
TempOutLt	Temporal Outer Left
TempOutR	Temporal Outer Right
TGFB1	Transforming growth factor-beta 1
UCVA	Uncorrected visual acuity
UHR OCT	Ultrahigh-resolution optical coherence tomography
UKPDS	United Kingdom Prospective Diabetes Study
VACM-1	Vascular cell adhesion molecule-1
VB	Venous beading
VEGF	Vascular endothelial growth factor
VEGFRs	Vascular endothelial growth factor receptors
VVO	Vasiculo-vacuolar organelles
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
%	Percent
µm	Micrometer
3D	3 dimensional
95%CI	95% Confidence Interval

Introduction

Diabetes mellitus is a worldwide pandemic disease. As of 2010, more than 200 million people had been diagnosed with diabetes, and this number is predicted to increase by 62% by 2025. This increase is due to an increase in obesity together with the increased life expectancy of the world population. DM complications include macroangiopathy (myocardial infarction or vasculocerebral stroke) and microangiopathy (diabetic nephropathy, neuropathy, and retinopathy) ***(Romero-Aroca et al., 2016).***

Diabetic retinopathy (DR) is the most common cause of blindness, affecting 1.9% of patients with DM. Furthermore, 2.64% of diabetic patients have visual sight-threatening diabetic retinopathy (STDR). The major cause of visual impairment in DM patients is diabetic macular edema (DME), with an annual incidence of 2.19%. DME is a consequence of DR in the macular area and is secondary to retinal barrier rupture, which is in turn secondary to a range of metabolic changes brought about by hyperglycemia ***(Romero-Aroca et al., 2016).***

Although the long-term effects of D.M on vascular tissues are very well known, its effect on retinal neurons isn't very clear ***(Königsreuther and Jonas, 1995).***

Normal vision depends on the normal function of retinal neurons so vision loss in diabetes must be explained in terms of altered neuronal function & functional changes in the vasculture ***(Lieth et al., 2000).***

Diabetic Retinopathy affects up to 80 % of all patients who have had diabetes for 10 years or more ***(Williams et al., 2004).***

The longer a person has diabetes, the higher chances of developing diabetic retinopathy ***(Chaill et al., 1997).***

It is known that diabetes damage glial cell & neuronal metabolism which directly impact neurotransmission & may lead to increase apoptosis of retinal neurons, glial cell reactivity, microglial activation & altered glutamate metabolism resulting in dysfunction & even degeneration of neuronal cells which in turn cause breakdown of blood-retinal barrier & lead to visual field defects ***(Lieth et al., 2000).***

Thinning of the total retina in type 1 diabetic patients with minimal retinopathy compared with healthy controls is attributed to a selective thinning of inner retinal layers and supports the concept that early DR includes a neurodegenerative component ***(van Dijk et al., 2009)***.

In 2002 Varkonyi, Peto & Degi reported the effect of metabolic control of diabetes on nerve fiber layer (NFL) they have demonstrated that NFL thickness tended to decrease with impairment of metabolic control in diabetic cases with & without ophthalmoscopically detectable retinopathy ***(Varkonyi et al., 2002).***

Ganglion cell layer (GCL) thinning in the pericentral area and corresponding loss of NFL thickness in the peripheral macula in patients with type 1 diabetes with no or minimal DR compared with control subjects. These results support the concept that diabetes mellitus (DM) has an early neurodegenerative effect on the retina, which occurs even though the vascular component of DR is minimal ***(van Dijk et al., 2010).***

If NFL thinning is significant in diabetic patients with preclinical diabetic retinopathy, evaluation of peripapillary NFL thickness would be very important ***(Chen et al., 2015)***, because early detection and treatment

of diabetic retinopathy is critical to reduce the risk of blindness ***(ETDRS research group, 1985).***

With the help of optical coherence tomography (OCT) , it is now possible to measure NFL thickness with a low- coherence light source projected onto the retina to determine retinal thickness which not only measures ganglion cell layer (GCL) axons but also muller cell processes & astrocytes to measure the effect of DM on NFL and GCL thickness ***(Jaffe and* Capriol*,2004).***

Periodic glycosylated haemoglobin (HbA1c) measurements can reflect the long-term control of hyperglycaemia. Intensive glycemic control had been proved to be effective in decreasing incidence rate of development and progression of diabetic retinopathy in type 1 and type 2 diabetic mellitus as demonstrates by diabetes control and complication trials ***(Moon et al., 2011).***