Clinical Significance of Serum Pigment Epithelium Derived Factor in Patients with Diabetic Retinopathy

Thesis

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الأهمية الإكلينيكية للعامل المُستمَد من الظهارة الملونة فى مرضى إعتلال الشبكية السكرى

رسالة

توطئة للحصول على درجة الماجستير فى الباثولوچيا الإكلينيكية و الكيميائية

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Summary and Conclusion

Diabetic retinopathy, a serious microvascular complication of DM, remains one of the leading causes of blindness throughout the world. It is characterized by microvascular damage and capillary non-perfusion resulting in retinal angiogenesis.

Pigment epithelium-derived factor (PEDF), a 50-kDa protein is a member of the serine protease inhibitor (serpin) family PEDF was first identified in the conditioned-medium of cultured human retinal pigment epithelial cells. It inhibits retinal endothelial cell growth, migration and suppresses ischemia-induced retinal neovascularization.

The aim of this work was to study the clinical significance of serum PEDF in patients with diabetes mellitus and its relevance of PEDF to the progression of diabetic retinopathy.

The present study was conducted on 60 diabetic patients who were recruited from the Ophthalmology Department at Ain Shams University Hospitals. The patients' group was divided according to the international severity scale into 4 subgroups; non-apparent diabetic retinopathy, mild-to-moderate non-proliferative, severe non-proliferative, proliferative diabetic retinopathy, each subgroup included 15 patients. Healthy control group included 20 healthy subjects.

List of Abbreviations

4-AAP	: 4-aminoantipyrine
ACE	: Angiotensin converting enzyme
AGE_S	: Advanced glycation end products
ANG II	: Angiotensin II
ANOVA	: Analysis of variation
AR	: Aldose reductase
Asp	: Aspartic acid
ATGL	: Adipose triglyceride lipase
ATP	: Adenosine tri-phosphate
AUC	: Area under curve
bFGF	: basic fibroblast growth factor
BRB	: Blood retinal barrier
CE	: Cholesterol esterase
CO	: Cholesterol oxidase
CTGF	: Connective tissue growth factor
DAG	: Diacylglycerol
DHAP	: Dihydroxyacetone phosphate
DHBS	: Dichloro-hydroxy benzene sulfonic acid
DM	: Diabetes Mellitus
DME	: Diabetic macular edema
DR	: Diabetic retinopathy
ECM	: Extracellular matrix

List of Abbreviations (Cont.)

EC_s	: Endothelial cells
ELISA	: Enzyme linked immunosorbent assay
eNOS	: endothelial nitric oxide synthase
ERG	: Electroretinogram
FA	: Fluorescein angiography
FasL	: Fas ligand
FGFR	: FGF receptor
FN	: False negative
FP	: False positive
GAPDH	: Glyceraldehyde 3-phosphate dehydrogenase
GFAT	: Glutamine fructose-6-phosphate amidotransferase
GK	: Glycerol kinase
Gln	: Glutamine
Glu	: Glucose
GLUT1	: Glucose transporter 1
GPO	: Glycero-phosphate oxidase
HA	: Hyaluronan
HBA_{1C}	: Glycated hemoglobin
HDL-C	: High density lipoproteins cholesterol
HRP	: Horseradish peroxidase
HSPGs	: Heparin sulphate proteoglycans

List of Abbreviations (Cont.)

HUVECs	: Human umbilical vein endothelial cells
Ia	: Non apparent diabetic retinopathy
Ib	: Mild-to-moderate non proliferative diabetic retinopathy
Ic	: Severe non proliferative diabetic retinopathy
ICAM-1	: Intracellular adhesion molecule-1
Id	: Proliferative diabetic retinopathy
IGF-1	: Insulin-like growth factor -1
IGF-1R	: IGF-1 receptor
IPF	: Idiopathic pulmonary fibrosis
IRMA	: Intraretinal microvascular abnormalities
LDL-C	: Low density lipoproteins cholesterol
MAP	: Mitogen activated protein
MMP_s	: Matrix metalloproteinases
MNPDR	: Mild-to-moderate non proliferative diabetic retinopathy
NADP	: Nicotinamide adenine dinucleotide phosphate
NADPH	: The reduced form of NADP
NF-kB	: Nuclear factor kappa-light-chain-enhancer of activated B cells
NPDR	: Non Proliferative diabetic retinopathy
NPV	: Negative predictive value

List of Abbreviations (Cont.)

OCT	: Optical coherence tomography
O-GlcNAc	: O-linked N-acetyl glucosamine
OGT	: O-linked N-acetyl glucosamine GlcNAc transferase
PA-1	: Plasminogen activator -1
PAI-1	: Plasminogen activator inhibitor – 1
PDGF	: Platelet-derived growth factor
PDR	: Proliferative diabetic retinopathy
PEDF	: Pigment epithelium derived factor
PKC	: Protein kinase C
PlGF	: Placental growth factor
PPV	: Positive predictive value
Pro	: Prolene
PVDF	: Polyvinylidene fluoride
QC	: Quality controls
RAGE	: Receptor for AGE
RAS	: Renin angiotensin system
RCL	: Reactive central loop
RGCs	: Retinal ganglion cells
ROC	: Receiver operating characteristic
ROS	: Reactive oxygen species
ROS	: Reactive oxygen species
RPE	: Retinal pigment epithelium

List of Abbreviations (Cont.)

SD	: Standard deviation
Serpin	: Serine protease inhibitor
SNPDR	: Severe non proliferative diabetic retinopathy
SOD	: Superoxide dismutase
SP1	: Specificity protein 1
SPSS	: Statistical program for social science
T1DM	: Type 1 diabetes mellitus
T2DM	: Type 2 diabetes mellitus
TC	: Total cholesterol
TG	: Triglycerides
TGF-β	: Transforming growth factor- β
TN	: True negative
TP	: True positive
UDP-GlcNAc	: Uridine diphosphate N-acetyl glucosamine
UPA	: Urokinase-type plasminogen activator
VCAM-1	: Vascular cell adhesion molecule-1
VEGF:	: Vascular endothelial growth factor
VEGFR	: VEGF receptor
VLDL	: Very Low density lipoproteins

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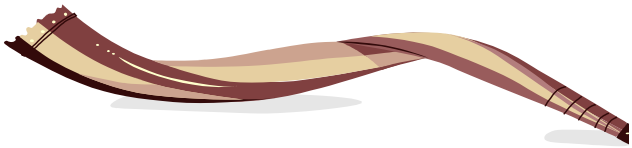


قَالُوا سُبْحَانَكَ
لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا
إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيمُ
صدق الله العظيم
سورة البقرة الآية
(٣٢)

Introduction

Diabetes mellitus is a chronic metabolic disease, characterized by hyperglycemia **(WHO, 2010).** The International Diabetes Federation estimates that 285 million people around the world have diabetes. This total number is expected to rise to 438 million within 20 years **(International Diabetes Federation, 2010).** Diabetic retinopathy, a serious microvascular complication of diabetes remains one of the leading causes of blindness throughout the world. It is characterized by microvascular damage and capillary non-perfusion resulting in retinal angiogenesis **(Fu et al., 2010).**

Angiogenesis in the retina is a complex multistep process which results in the formation of new vessels due to the imbalance between the angiogenic stimulators and inhibitors. Many endogenous inhibitors including endostatin, angio-statin and pigment epithelium-derived factor (PEDF) have been reported **(Noma et al., 2002).**

Pigment epithelium-derived factor (PEDF), a 50-kDa protein, is a member of the serine protease inhibitor (serpin) family **(Ogata et al., 2007).** PEDF was first identified in the conditioned-medium of cultured human retinal pigment epithelial cells, and it inhibits retinal endothelial cell growth, migration and suppresses ischemia-induced retinal neovascularization **(Katakami et al., 2008 and Matsuyama et al., 2008).**