



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم



MONA MAGHRABY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



MONA MAGHRABY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغييرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



MONA MAGHRABY

Serum Glucagon like peptide 1 Level and Peripheral Vascular Disease in Patients with Type 2 Diabetes

*Thesis
Submitted for partial fulfillment of master Degree
In Endocrinology and metabolism*

By
Ahmed Abe Bakr El Sayed Ibrahim
MBBCH

Supervised by

Prof. Dr. Rania Sayed Abd El Baki
Prof. of Internal Medicine and Endocrinology
Faculty of Medicine Ain-Shams University

Ass. Prof. Dr. Merhan Sami Nasr
Ass. Prof. of Internal Medicine and Endocrinology
Faculty of Medicine Ain-Shams University

Dr. Bassem Murad Mostafa
Lecturer of Internal Medicine and Endocrinology
Faculty of Medicine Ain-Shams University

Faculty of Medicine
Ain Shams University
2020

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

فَتَعَالَى اللَّهُ الْمَلِكُ الْحَقُّ وَلَا تَعْجَلْ بِالْقُرْآنِ مِنْ قَبْلِ أَنْ يُقْضَىٰ إِلَيْكَ وَحْيُهُ

وَقُلْ رَبِّ زِدْنِي عِلْمًا

طه. (114)

Acknowledgement

Thanks to Allah

I would like to express my deepest indebtedness, gratitude and sincere appreciation to Prof. Dr, **Rania Sayed Abd El Baki** Professor of Internal Medicine and Endocrinology, Faculty of medicine, Ain Shams University, for suggesting the subject, her valuable help, kind advice and close supervision during all steps of this work. She spared no time or effort providing me the constructive guidance which has a paramount axis in the initiation and progression of this work. It was great honor to me to do this study under her supervision.

My deepest appreciation goes to **Ass. Prof. Dr. Merhan Sami Nasr**, Assistant Professor of Internal Medicine and Endocrinology, Faculty of Medicine, Ain Shams University, for her cooperation, encouragement and continuous support. She kindly supervised and revised all the details of the work. I would like to express my thanks for her endless patience with me and wise opinions and for her precious time and effort that made this study possible.

I owe special feeling of gratitude to **Dr. Bassem Murad Mostafa**, Lecturer of Internal Medicine and Endocrinology, Faculty of Medicine, Ain Shams University who generously aided and directed me. Many thanks for his encouragement, supervision, cooperation, and helpful suggestions. He followed the procedures of the work with indispensable support, devotion.

List of Contents

Contents

List of Tables	I
List of Figures	II
List of Abbreviations	III
Introduction	1
Aim of the Work	2
Review of Literature	
1. Glucagon like peptide-1	3
2. Type 2 diabetes mellitus and peripheral vascular disease	22
3. Glucagon like peptide-1 and peripheral vascular disease	44
Subjects and Methods	57
Results	63
Discussion	81
Summary and Conclusion	89
Recommendations	93
References	94
Arabic Summary	

List of Tables

Table	Title	Page
1	Main characteristics of therapy with GLP-1 receptor agonists in Type 2 Diabetes	19
2	Classification of diabetes	26
3	Criteria for the diagnosis of diabetes:	27
4	Glycemic recommendations for many non-pregnant adults with diabetes	32
5	Classification of PAD	40
6	Characteristics of the study population	67
7	Descriptive data for all studied groups	67
8	Comparing studied groups as regard gender using chi square test	68
9	Comparison between two groups regarding all data using Unpaired t test	77
10	Descriptive Statistics of APSV (in Group 2)	77
11	Correlation between GLP1 versus other variables among all subjects.	78

List of Figures

Figure	Title	Page
1	Glucose, insulin and incretin effect.	6
2	The tissue-selective processing of proglucagon.	8
3	GLP-1 mediated insulin secretion in the b-cell.	11
4	GLP-1 is released from the gut after meal ingestion	15
5	The metabolic effects of GLP-1.	16
6	Hormone responses to oral glucose	17
7	Structure of native GLP-1 and the approved GLP-1 receptor agonists	19
8	Genetic and environmental risk factors impact inflammation, autoimmunity, and metabolic stress.	23
9	Schematic representation of the response to ischemia in peripheral artery disease	38
10	The metabolic abnormalities that characterize diabetes	39
11	Direct and Indirect Actions of GLP-1 in the Heart and Blood Vessels	44
12	The vascular biology of GLP-1 action	45
13	Mechanisms Linking GLP-1 to Modulation of Inflammation	53
14	the major direct actions of GLP-1	54
15	Percent of males and females in all studied groups.	67
16	Comparing studied groups as regard gender	68
17	Comparing studied groups as regard age	69
18	Comparing studied groups as regard BMI	70
19	Comparing studied groups as regard Systolic blood pressure	71
20	Comparing studied groups as regard diastolic blood pressure	72
21	Comparing studied groups as regard FBS	73
22	Comparing studied groups as regard 2h PPBG	74
23	Comparing studied groups as regard HbA ₁ C	75
24	Comparing studied groups as regard GLP1	76
25	Correlation between GLP-1 and BMI	78
26	Correlation between GLP-1 and FBS	79
27	Correlation between GLP-1 and 2h PPBG	79
28	Correlation between GLP-1 and HbA ₁ C	80
29	Correlation between GLP-1 and APSV (in Group 2 {cases})	80

List of Abbreviations

2HPPG	2 hours postprandial glucose
ABI	Ankle-brachial index
AC	adenylate cyclase
AGEs	advanced glycation end products
AIDS	Acquired immunodeficiency syndrome
ALI	Acute limb ischemia
AMPK	adenosine monophosphate activated protein kinase
APSV	ankle peak systolic velocity
ASCVD	Atherosclerotic cardiovascular disease
ATII	angiotensin II
ATP	adenosine tri phosphate
BBB	blood brain barrier
BID	twice daily
CAD	coronary artery disease
cAMP	cyclic adenylyl monophosphate
cGMP	cyclic guanosine monophosphate
CICR	calcium-induced calcium release
CLI	critical limb ischemia
CNS	central nervous system
CVD	cardiovascular disease
DM	diabetes mellitus
DPP-4	dipeptidylpeptidase-4

ECD	Endothelial cell dysfunction
ECs	endothelial cells
EECs	enteroendocrine cells
eNOS	endothelial nitric oxide synthase
Epac2	exchange protein activated by cAMP
FBG	fasting blood glucose
GDM	Gestational diabetes
GHRH	growth hormone releasing hormone
GIP	glucose- dependent insulino-tropic polypeptide.
GLP- 1R	glucagon like peptide 1 receptor
GLP 2	Glucagon Like Peptide 2.
GLP-1	glucagon-like peptide 1.
GLUT1/2	glucose transporter 1/2
GRPP	glicentin-related polypeptide
hbA1C	glycated hemoglobin
HIF	hypoxia inducible factor
HIV	human immunodeficiency virus
hVECs	human vascular endothelial cells
IC	intermittent claudication
ICAM-1	intracellular adhesion molecule1
IELs	Intestinalintraepithelial lymphocytes
IL-1	interleukin-1
IP-1	intervening peptide-1
IP-2	intervening peptide-2
MCP-1	Monocyte Chemattractant protein-1
MEG-1	megakaryocyte-1

MI	myocardial infarction
MODY	maturity-onset diabetes of the young
MPGF	major proglucagon fragment
MRA	magnetic resonance angiography
mRNA	messenger ribonucleic acid
NF-KB	nuclear factor kappa B
NO	nitric oxide
NSGP	National Glycohemoglobin Standardization Program
NTS	nucleus tractus solitari
OGTT	oral glucose tolerance test
PAD	peripheral arterial disease
PAI-1	plasminogen activator inhibitor-1
PC1/3	prohormone convertase 1/3
PC2	prohormone convertase2
PCSK1	prohormone convertase subtilisin-kexin 1
PCSK2	prohormone convertase subtilisin-kexin 2
PDR	proliferative diabetic retinopathy
Pdx-1	pancreatic and duodenal homeobox 1
PG	prostaglandin
PI3K	phosphatidylinositol-3 kinase
PKA	protein kinase A
PKB	protein kinase B
PTH	parathyroid hormone
PVD	peripheral vascular disease
QW	once weekly

RAGE	Receptor for advanced glycation end products
ROS	reactive oxygen species
SGLT2	sodium glucose transporter 2
SIRT6	sirtuin6
SMCs	smooth muscle cells
TBI	tibial-brachial index
TcPO2	Transcutaneous Oxymetry
TF	tumor necrosis factor
TNF α	tumour necrosis factor α
VAM	vascular adhesion molecule
VCAM-1	vascular cell adhesion molecule 1
VECs	Vascular Endothelial Cells
VEGF	vascular endothelial growth factor
VSMCs	Vascular Smooth Muscle Cells
WBCs	white blood cells

Introduction



Introduction

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control (*Grant and Kirkman, 2015*).

GLP-1 is synthesized and secreted from enteroendocrine L cells found throughout the small and large intestine. GLP-1 increases insulin and inhibits glucagon secretion in a glucose-dependent manner. GLP-1 also stimulates beta cell proliferation and neogenesis, and inhibits beta cell apoptosis (*Jonathan et al., 2013*).

GLP1 has several actions in both diabetics and healthy individuals, mediated through receptor (GLP1-R) which is present abundantly in endothelial cells and vascular smooth muscle cells (*Sleiman and Azar ,2012*). Recently both GLP1 and its metabolite were found to have a glucose independent vasorelaxant effects (*Sleiman and Azar ,2012*).

Peripheral arterial disease (PAD) in people with type 2 diabetes mellitus (T2DM) exhibits broad clinical characteristics and various consequences and is known as one of the major macrovascular complications of T2DM, the prevalence of which is on the rise. Atherosclerosis is recognized as the most direct and important cause of PAD (*Sang and Young, 2015*).

Ankle Peak Systolic Velocity (APSV) is the mean of the peak systolic velocities measured across the distal tibial arteries at the ankle level during arterial duplex scanning of the lower extremities (*Bishara, et al., 2009*).