STUDY OF GLUCAGON LIKE PEPTIDE -1 IN PATIENTS WITH ISCHEMIC HEART DISEASE

Thesis

Submitted for Partial Fulfillment of Master Degree
in Internal Medicine

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2011

دراسة البروتين المشابه لهرمون الجلوكاجون -١ فى مرضى قصور الشريان التاجى

رسالة

مقدمة من
الطبيب/ بولس عزمى بولس
بكالوريوس الطب والجراحة

توطئه للحصول علي درجة الماجستير في الباطنة العامة

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Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreated by L cells of the GIT in response to nutrient intake and plays a major role in glucose homeostasis by stimulating insulin secretion, suppressing glucagon secretion, inhibiting gastric emptying, and reducing appetite and food intake. This hormone exerts its effects through interaction with G-protein coupled receptors. The GLP-1 receptor is widely expressed throughout the body (a- and P-cells in the islets of pancreas, other parts of the gastrointestinal tract, central and peripheral nervous systems, heart, kidney, and the lung).

In patients with type 2 diabetes mellitus, the incretin effect is reduced or even absent due to significant, reduction in meal-stimulated levels of GLP-1. Therapeutic efforts have been focused on the development of GLP-1 receptor agonists, which would appear to be ideal therapeutic agents for use in patient with type 2 diabetes. Incretin mimetics, exenatide and liraglutide, which are GLP-1 receptor agonists resistant to DPP- IV degradation, and the DPP-IV inhibitors (the gliptins), which potentiate the effect of the endogenously secreted incretin hormones by competitively inhibiting the enzyme responsible for their degradation

The incretin mimitics have effects extending beyond their

ACKNOWLEDGMENTS

*First and above all, thanks to **ALLAH**, the source of all knowledge and wisdom who enabled me to complete this work.*

*I wish to express my deep and sincere gratitude to **Prof. Dr. Nermin Ahmed Sheriba**, Professor of Internal Medicine and Endocrinology, Faculty of Medicine-Ain Shams University. Her wide knowledge and logical way of thinking have been of great value for me. Her understanding, encouraging and personal guidance have provided a good basis for the present study. No words of thanks could ever express my feelings towards her extreme support.*

*I am deeply grateful to **Prof. Dr. Salwa Sedik Hosny,** Assistant Professor of Internal Medicine and Endocrinology, Faculty of Medicine-Ain Shams University, for her inspiration, sincere care, follow up, encouragement and important support throughout this work., her sincere directions were of great value in this research.*

*I wish to express my warm and sincere thanks to **Dr. Matta Makram Anees,** Lecturer of Internal Medicine and Endocrinology, Faculty of Medicine-Ain Shams University, for his kind help in this research.*

*Also I wish to express many thanks to **Dr. Maram Mohammed Maher** Lecturer of Internal Medicine and Endocrinology, Faculty of Medicine-Ain Shams University, for her kind support, instructions and help.*

*Lastly I would like to extend my warm thanks to **Dr. Magdy Abbas Abdel Aziz** Assistant consultant of biochemistry Ain Shams University Hospitals, for his hard work in laboratory investigations of this work.*

CONTENTS

List of Abbreviations

ACTH	Adrenocorticotropin hormone.
ACCORD	Action to control cardiovascular risk in diabetes
ADA	American diabetes association.
AGEs	Advanced glycation end products
AHA	American heart association
AMI	Acute myocardial infarction.
AMP	Adenosine monophosphate.
AMPK	AMP-activated protein kinase.
Ach	Acetylcholine
ANOVA	Analysis of variance
ATP	Adenosine triphosphate.
BMI	Body mass index.
CABG	Coronary artery bypass graft.
CAD	Coronary artery disease.
cAMP	Cyclic AMP.
cAMP-GEFII	cAMP-regulated guanine nucleotide exchange factor II.
CHF	Congestive heart failure.
CD26	Dipeptidyl peptidase IV.
CVA	Cerebrovascular accident.
CHF	Congestive heart failure.
Chol.	Cholesterol.
CRH	Corticotrophin-releasing hormone.
CRP	C-reactive protein
CYP	Cytochrome pathway
CV	Cardiovascular.
CVD	Cardiovascular disease.

CPAP	Continous positive airway pressure
CHD	Coronary heart disease.
D DM	Duration of diabetes.
DSE	Dobutamine stress echocardiography
Dias. BP	Diastolic blood pressure.
DNA	Deoxyribonucleic acid.
DPP-IV	Dipeptidyl peptidase IV.
eNOS	Endogenous nitric oxide synthase
ECG	Electrocardiogram.
ECHO	Echocardiogram.
EF	Ejection fraction.
ELIZA	Enzyme linked immunosorbant assay.
Epac2	cAMP-regulated guanine nucleotide exchange factor II.
ED	Endothelial dysfunction.
FBG	Fasting blood glucose.
FMD	Flow mediated dilatation.
FDA	FOOD and drug association
GIP	Gastric inhibitory polypeptide / Glucose dependent insulinotropic polypeptide.
GLP-1	Glucagon like peptide-1.
GLP-1r	GLP-1 receptors.
GLP-2	Glucagon like peptide-2.
GPCR-kinase	G-protein-coupled receptor kinase.
GRP	Gastrin releasing peptide.
GRPP	Glicentin related pancreatic polypeptide.
GLUT	Glucose transporter.
HbA_{1C}	Glycated hemoglobin / hemoglobin A_{1C}.
HDL	High density lipoprotein.
His.	Histidine
HF	Heart failure
HR	Hazard ratio.
IL-1	Interleukin-1.

IP-1	Intervening peptide-1
IP-2	Intervening peptide-2
IR	Insulin resistance.
IDF	International diabetes foundation.
ICAM	Intracellular adhesion molecule.
LDL	Low density lipoprotein.
LV	Left ventricle.
LVEF	left ventricular ejection fraction.
MAPK	Mitogen-activated protein kinase.
mRNA	Messenger ribonucleic acid.
MPGF	Major proglucagon fragment.
MDP-1	Monocyte chemotactic protein-1
NMR	Neuclear magnetic resonance.
NCEP	National cholesterol education programme
NO	Nitric oxide
NPV	Negative peridictive value.
NYHA	New York heart association.
OSA	Obstructive sleep apnea
OGTT	Oral glucose tolerance test
P	P-value / probability
PAI	Plasminogen activator inhibitor
PG	proglucagon
PCI	Percautanous coronary intervention
PK	Protein kinase
PERISCOPE	Pioglitazone effect on regression of intravascular sonographic coronary obstruction prospective evaluation
PC	Proglucagon convertase
PKA	Protein kinase A.
PPAR	Peroxisome proliferators activator receptor.
PVN	Paraventricular nucleus.
PPV	Positive peridictive value
PYY	Peptide YY / Peptide Tyrosine Tyrosine.

r	Pearson's correlation coefficient.
RAS	Renin angiotensin aldosterone system.
RECORD	Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes.
RNA	Ribonucleic acid.
RAGEs	Receptors of advanced glycation end products
ROS	Reactive oxygen species.
ROC	Receiver operator characteristic.
Sc	Subcutaneous.
SD	Stander deviation.
Sig.	Significance.
SNS	Sympathetic nervous system.
SNP	Single nucleotide polymorphism.
SPSS	Statistical program for social science.
SR	Sarcoplasmic reticulum.
SS	Somatostatin.
SAS	Sleep apnea syndrome
Sys. BP	Systolic blood pressure.
T2DM	Type 2 diabetes mellitus.
TG	Triglycerides.
TF	Tissue factor
TNF	Tumor necrosis factor.
TZD	Thiazolidinediones
UKPDS	United kingdom prospective diabetes study
VSMC	Vascular smooth muscle cells
VLDL	Very low density lipoproteins
VP	Valine pyrrolide
$\mathbf{X^2}$	Chi-square test.

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Introduction

Glucagon-like peptide-1(GLP-1), is a gut incretin hormone that stimulates insulin secretion and also activates anti apoptotic signaling pathways in pancreatic cells **(*Bose et al., 2005).*** Glucagon-like peptide-1 has been shown to exert a direct cytoprotective effect via inhibition of apoptosis directly in target cells expressing the GLP-1 receptors **(*Redondo et al., 2003*).** It has been demonstrated that GLP-1 has receptors in the heart through which it exerts physiologically important effects on cardiac function **(*Holst, 2007)***. In the resting state, GLP-1 may inhibit the myocardial contractility, but after cardiac injury GLP-1 has constantly increased myocardial performance. It enhances insulin secretion and may enhances myocardial performance via the combined effects of enhanced insulin secretion and stimulation of p70sb kinase pathway **(*Zarich, 2005).***

GLP-1 has been shown to markedly reduce post prandial levels of glucose, triglycerides and free fatty acids and increase HDL levels in diabetics and non diabetic subjects. With this ability to reduce postprandial glucose excursion, it could be a promising agent for improving cardiovascular prognosis ***(Riddle and Drucker, 2006)***.

It is important to demonstrate that the effects of GLP-1 are not restricted to the pancreas and the gastrointestinal tract. In patients with heart failure, GLP-1 when given intravenously has been shown to improve the ejection fraction and regional wall scores trough its cardiac receptors, dilate the pulmonary artery and has a diuretic effect **(*Sokos et al., 2006).*** Patients with type 2 diabetes mellitus are considered at high risk for cardiovascular disease. **(*Song and Hardisty, 2008*)** and are characterized by a deficiency of GLP-1 **(*Nauck et al., 2004*)**.

Whether the GLP-1 deficiency is the link between type 2 diabetes mellitus and the development of ischaemic heart disease in need for further study.

Aim of the work

To measure the plasma levels of GLP-1 in patients with ischemic heart disease, both those with type 2 diabetes mellitus and those who are non- diabetic and to assess the role of GLP-1 in the development of ischemic heart disease.

Subjects and Methods

- **Subjects**

This study will be conducted on 54 subjects who will be selected from the outpatient clinic of cardiology department and the endocrinology unit of internal medicine departement, Ain