

Study of Glucagon Like Peptide – 1 in Patients with Congestive Heart Failure

Thesis

Submitted for Partial Fulfillment of Master Degree in
Endocrinology and Metabolism

By

Ahmed Mohammed Abd-El Fatah Hamam
M.B., B.CH

Supervised by

Prof. Dr. Nermin Ahmed Sheriba
Professor of Internal Medicine & Endocrinology
Faculty of Medicine
Ain Shams University

Dr. Khaled Mahmoud Makbol
Lecturer of Internal Medicine & Endocrinology
Faculty of Medicine
Ain Shams University

Dr. Mona Mohammed Abd-Elsalam
Lecturer of Internal Medicine & Endocrinology
Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University
2010

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

(قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْحَكِيمُ)

(سورة البقرة: ٣٢)

Dedication

My work is dedicated to:

My dear Family.

ACKNOWLEDGMENTS

First of all thanks to **ALLAH** who gives us the gift of knowledge and understand.

I would like 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 her 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 **Dr. Khaled Mahmoud Makbol**, Lecturer of Internal Medicine and Endocrinology, Faculty of Medicine-Ain Shams University, for his detailed and constructive comments, and for his important support throughout this work.

I wish to express my warm and sincere thanks to **Dr. Mona Mohamed Abd-Elsalam**, Lecturer of Internal Medicine and Endocrinology, Faculty of Medicine-Ain Shams University, who offered much of her time and advice through my work in this study. Her kind assistance, great support and sincere cooperation have been of great value in this study.

Lastly but not least I would like to extend my warm thanks to all my professors, staff members and colleagues in the Kobry El Kobba Military Hospital for their continuous help and support.



CONTENTS

	Page
Acknowledgment	I
List of abbreviations	II
List of figures	V
List of tables	VIII
Protocol	X
<hr/>	
Review of literature	
Chapter 1:	
Glucagons like peptide – 1.	1
Chapter 2:	
Metabolic mechanisms in heart failure.	28
Chapter 3:	
The role of incretins in cardiovascular control	52
<hr/>	
Subjects and methods	72
Results	78
Discussion	110
Summary and conclusions	116
Recommendations	121
References	123
Arabic summary	



List of Abbreviations

ACTH	Adrenocorticotropin.
Acyl CoA	Acyl coenzyme A
ADA	American diabetes association.
AMI	Acute myocardial infarction.
AMP	Adenosine monophosphate.
AMPK	AMP-activated protein kinase.
Angio-II	Angiotensin-II.
ANOVA	Analysis of variance
ATP	Adenosine triphosphate.
BMI	Body mass index.
BNP	Brain natriuretic peptide.
CABG	Coronary artery bypass graft.
CAD	Coronary artery disease.
cAMP	Cyclic AMP.
cAMP-GEFII	cAMP-regulated guanine nucleotide exchange factor II.
CAT	Carnitine acyl translocase.
CCB	Calcium channel blocker.
CD26	Dipeptidyl peptidase IV.
cGMP	Cyclic guanosine monophosphate
CHF	Congestive heart failure.
Chol.	Cholesterol.
CK	Creatine kinase.
CPT-1	Carnitine palmitoyltransferase-1
CRP	Corticotrophin-releasing hormone.
CRT	Cardiac resynchronization therapy
CV	Cardiovascular.
CVD	Cardiovascular disease.
CXR	Chest X-ray.
D DM	Duration of diabetes.
Dias. BP	Diastolic blood pressure.
DNA	deoxyribonucleic acid.
DPP-IV	Dipeptidyl peptidase IV.
ECG	Electrocardiogram.
ECHO	Echocardiogram.
EF	Ejection fraction.
ELIZA	Enzyme linked immunosorbant assay.



List of Abbreviations

Epac2	cAMP-regulated guanine nucleotide exchange factor II.
FAO	Fatty acid oxidation.
FBG	Fasting blood glucose.
FFA	Free fatty acids.
FMD	Flow mediated vasodilatation.
GH	Growth hormone.
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} .
HCL	Hydrogen chloride.
HDL	High density lipoprotein.
HF	Heart failure
IGF-1	Insulin-like growth factor-1.
IP-1	Intervening peptide-1
IP-2	Intervening peptide-2
IR	Insulin resistance.
IRCM	Insulin-resistant cardiomyopathy
IRS	Insulin receptor substrate.
KBs	Ketone bodies.
LDL	Low density lipoprotein.
LV	Left ventricle.
LVEF	left ventricular ejection fraction.
LVH	Left ventricular hypertrophy.
MAPK	Mitogen-activated protein kinase.
MHD	multiple hormonal and metabolic deficiency syndrome
MPGF	Major proglucagon fragment.
mRNA	Messenger RNA.
NSAID	Non-steroidal anti-inflammatory drug.
NYHA	New York heart association.
Ox phos	Oxidative phosphorylation.
P	P-value / probability
PCr	Phosphocreatine.
PDH	Pyrovate dehydrogenase.
PET	Positron emission tomographic.



List of Abbreviations

PGC-1 α	PPAR γ coactivator 1 α .
PKA	Protein kinase A.
PPAR	Peroxisome proliferators activator receptor.
PVN	Paraventricular nucleus.
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.
ROS	Reactive oxygen species.
SA-HRP	Streptavidin-horseradish peroxidase.
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.
Sys. BP	Systolic blood pressure.
T2DM	Type 2 diabetes mellitus.
TG	Triglycerides.
TMB	Tetramethylbenzidine.
TMZ	Trimetazine.
TNF	Tumor necrosis factor.
TZD	Thiazolidinediones
UCP	Uncoupled protein.
VO _{2max}	Peak oxygen consumption.
X ²	Chi-square test.



List of Figures

	Page
A. Figures of the Review:	
Figure (1) Alternative posttranslational processing of proglucagon and the transcription of proglucagon gene.	3
Figure (2) 2D-NMR structure of GLP-1.	6
Figure (3) L cell.	7
Figure (4) Factors involved in the control of the activity of L cells.	9
Figure (5) Plasma concentrations of insulin, GLP-1 (total) and GIP (total) during the day time in healthy subjects.	11
Figure (6) GLP-1 and glucose signaling.	13
Figure (7) Summary of cellular actions of GLP-1 that lead to stimulation of insulin secretion.	16
Figure (8) The neural pathway of the action of GLP-1	19
Figure (9) Structure of native GLP-1, exenatide, liraglutide, sitagliptin and vildagliptin.	26
Figure (10) Proposed concept of metabolic vicious circle in HF.	30
Figure (11) Relationships/mechanisms linking insulin resistant to HF.	34
Figure (12) Heart failure invokes compensatory SNS and RAS activation.	32
Figure (13) Multiple defects of energy transfer in HF.	36
Figure (14) Free fatty acids metabolism in HF	38
Figure (15) Recommendation regarding thiazolidinediones use and HF.	48
Figure (16) Glycemic and extraglycemic effects of incretins agents.	54
Figure (17) Proposed antihyperglycemic strategy in patient with T2DM and Coronary artery disease.	69
Figure (18) Proposed antihyperglycemic strategy in patient with T2DM and HF.	71



	Page
B. Figures of the Results:	
Figure (1)	Sex distribution between groups. 97
Figure (2)	Pie chart showing NYHA classification in group 1. 97
Figure (3)	Pie chart showing NYHA classification in group 1. 98
Figure (4)	Comparison of GLP-1 in all groups. 98
Figure (5)	Statistical comparisons GLP-1 in all groups. 99
Figure (6)	Comparison between fasting plasma GLP-1 between NYHA classification in all studied subjects. 99
Figure (7)	Correlation between fasting GLP-1 and duration of DM in all studied groups. 100
Figure (8)	Correlation between fasting GLP-1 and systolic blood pressure in all studied groups. 100
Figure (9)	Correlation between fasting GLP-1 and diastolic in all studied groups. 101
Figure (10)	Correlation between fasting GLP-1 and fasting blood glucose in all studied groups. 101
Figure (11)	Correlation between fasting GLP-1 and 2 h postprandial blood glucose in all studied groups. 102
Figure (12)	Correlation between fasting GLP-1 and HbA _{1C} in all studied groups. 102
Figure (13)	Correlation between fasting GLP-1 and ejection fraction in all studied groups. 103
Figure (14)	Correlation between fasting GLP-1 and NYHA classification in all studied groups. 103
Figure (15)	Correlation between fasting GLP-1 and HbA _{1C} in group 2. 104
Figure (16)	Correlation between fasting GLP-1 and NYHA classification in group 2. 104
Figure (17)	Correlation between fasting GLP-1 and HbA _{1C} in group 3. 105
Figure (18)	Correlation between fasting GLP-1 and HbA _{1C} in all diabetic patients. 105



	Page
Figure (19) Correlation between fasting GLP-1 and NYHA in all diabetic patients.	106
Figure (20) Correlation between fasting GLP-1 and duration of diabetes in all patients with CHF.	106
Figure (21) Correlation between fasting GLP-1 and fasting blood glucose in all patients with CHF.	107
Figure (22) Correlation between fasting GLP-1 and 2h postprandial blood glucose in all patients with CHF.	107
Figure (23) Correlation between fasting GLP-1 and HbA _{1C} in all patients with CHF.	108
Figure (24) Correlation between fasting GLP-1 and fasting blood glucose in all hypertensive patients.	108
Figure (25) Correlation between fasting GLP-1 and 2h blood glucose in all hypertensive patients.	109
Figure (26) Correlation between fasting GLP-1 and HbA _{1C} in all hypertensive patients.	109



List of Tables

Page**A. Tables of the Review:**

Table (1)	Effects on ATP-to-oxygen ratio of a total change from glucose to FFA utilization by myocardium.	37
Table (2)	Potential treatments for insulin-resistant cardiomyopathy.	42
Table (3)	The targets and their corresponding therapeutic agents for the metabolic modification of insulin-resistance in heart failure.	43

B. Tables of the results:

Table (1)	Sex distribution in all studied groups.	88
Table (2)	NYHA classification of cases with CHF (group1 and group 2).	88
Table (3)	Comparison between the different studied groups as regard their demographic data and investigations using ANOVA.	88
Table (4)	Comparison between group1 and group 4 regarding some studied parameters using independent –sample T test.	89
Table (5)	Comparison between group1 and group 2 regarding some studied parameters using independent –sample T test.	89
Table (6)	Comparison between group2 and group 4 regarding some studied parameters using independent –sample T test.	89
Table (7)	Comparison between group 3 and group 4 regarding some studied parameters using independent –sample T test.	90
Table (8)	Comparison between group1 and group 3 regarding some studied parameters using independent –sample T test.	90



	Page
Table (9) Comparison between all diabetics and nondiabetics regarding some studied parameters using independent sample T test.	90
Table (10) Comparison between all patients with CHF and those without CHF regarding some studied parameters using independent sample T test.	91
Table (11) Comparison between all hypertensives and non hypertensives regarding some studied parameters using independent sample T test.	91
Table (12) Independent sample T test between NYHA classification and GLP-1.	92
Table (13) Correlation between fasting plasma GLP-1 and all studied parameters in all groups.	92
Table (14) Correlation between fasting plasma GLP-1 and all studied parameters in group 1.	93
Table (15) Correlation between fasting plasma GLP-1 and all studied parameters in group 2.	93
Table (16) Correlation between fasting plasma GLP-1 and all studied parameters in group 3.	94
Table (17) Correlation between fasting plasma GLP-1 and all studied parameters in group 4.	94
Table (18) Correlation between fasting plasma GLP-1 and all studied parameters in all diabetics.	95
Table (19) Correlation between fasting plasma GLP-1 and all studied parameters in patients with CHF.	95
Table (20) Correlation between fasting plasma GLP-1 and all studied parameters in hypertensive patients.	96
Table (21) Stepwise regression analysis; Dependent variable: fasting plasma GLP-1.	96

Protocol



Introduction

Glucagon - like peptide-1 (GLP-1) is a naturally occurring incretin with both insulintropic and insulinomimetic properties. (**Sokos et al., 2006**). It is produced from the proglucagon gene in L-cells of the small intestine and is secreted in response to nutrients (**Dugan and Buse, 2005**).

GLP-1 exerts its main effect by stimulating glucose dependent insulin release from the pancreatic islets. It restores both first phase and second phase insulin response to glucose (**Fehse et al., 2005**). It has also been shown to slow gastric emptying, inhibit inappropriate post meal glucagon release, and reduce food intake (**Holst, 2007**).

GLP-1 receptors are G protein-coupled receptors (**Mayo et al., 2003**). The receptors are widely distributed in pancreatic islets, brain, heart, kidney and the gastrointestinal tract (**Alvarez et al., 2005**); it was established that there are GLP-1 receptors in the heart through which GLP-1 exerts physiological important effects on the heart (**Holst, 2007**).

In normal circumstances, the heart use non-esterified fatty acids as its "substrate of choice" for the production of ATP. After injury or stress, the heart shifts to using glucose as the substrate because it's energetically more efficient. However, once left ventricular dysfunction has progressed to sever dilated cardiomyopathy, the heart becomes insulin resistant, compromising the requirement for glucose. GLP-1 improves the efficiency of glucose uptake and utilization in the heart. GLP-1 infusion significantly improves left ventricular ejection fraction (**Sokos et al., 2006**).

In basal state, GLP-1 may inhibit contractility but after cardiac injury GLP-1 has constantly increase myocardial performance via the