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

Thesis
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بسم الله الرحمن الرحيم

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

(سورة البقرة:٣٢)

Dedication

My work is dedicated to:

My dear Family.

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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.

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.

PGC-1α	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.

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Introduction

Glucagon - like peptide-1 (GLP-1) is a naturally occurring incretin with both insulinotropic 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