Serum Levels of Fibroblast *Growth Factor-21 (FGF-21) in Coronary Heart Disease*

Thesis

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Abbreviations	
ACS	Acute Coronary Syndrome
AKT	Referred to type of mice that develops spontaneous Thymic Lymphomas (Akt = protein kinase B)
AN	Anorexia Nervosa
BAT	Brown Adipose Tissue
BMI	Body mass Index
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
cAMP	Cyclic Adenosine Mono Phosphate
cDNA	Complementary Deoxyribonucleic Acid
CMECs	Cardiac Microvascular Endothelial Cells
CHD	Coronary Heart Disease
CIP	Cerulein-Induced Pancreatitis
CK	Creatine Kinase
CKD	Chronic Kidney Disease
DAG	Diacylglycerol
DBP	Diastolic blood pressure
DM2	Diabetes Mellitus type 2
ECG	Electrocardiogram
ED	Emergency Department
ER	Endoplasmic Reticulum
ERK	Extracellular-signal-Regulated Kinase

Erm protein	Ezrin–Radixin–Moesin proteins
ESRD	End-Stage Renal Disease
Etv4	E- Twenty six (ETS)translocation variant 4
Etv5	E- Twenty six (ETS)translocation variant 5
FBG	Fasting Blood Glucose
Fbg	Fibrinogen
FFA	Free Fatty Acid
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
Frs2α	FGFR substrate -2 α
GDP	Guanosine Diphosphate
GGT	γ-Glutamyltransferase
GH	Growth Hormone
GLUT1	Glucose Transporter 1
GLUT4	Glucose Transporter 4
Grb2	Growth factor receptor-bound 2
GTN	Glyceryl trinitrate
GTP	Guanosine Triphosphate
HBS	Heparan sulfate Binding Site
HDLc	High Density Lipoproteins cholesterol
HMG-CoA	3- Hydroxy 3-Methyl Glutaryl- CoA
HOMA-IR	Homeostasis Model of Assessment- Insulin Resistance
HOMA-IS	Homeostasis Model of Assessment- Insulin Sensitivity
HS	Heparan Sulfate

HSPG	Heparan Sulphate Proteoglycan
ICAM	Intercellular Adhesion Molecule
Ig	Immunoglobulin
IGF-1	Insulin-like Growth Factor 1
IHD	Ischemic Heart Disease
IL	Interleukin
IMA	Ischemia Modified Albumin
IP3	Inositol-1, 4, 5-triphosphate
KLB	β-Klotho
KO mouse	Knockout *mouse*
LADA	Latent Autoimmune Diabetes in Adults
LDLc	Low Density Lipoproteins cholesterol
MAP	Mitogen Activated Protein
MAPK	Mitogen-Activated-Protein Kinase
MEK	Mitogen Activated Protein kinase kinase
MetS	Metabolic Syndrome
MI	Myocardial Infarction
MIDCAB	Minimally Invasive Direct Coronary Artery Bypass
MKP3	MAPK phosphatase 3
MPO	myeloperoxidase
MMP	Matrix Metalloproteinases
MR	magnetic resonance
mRNA	Messenger Ribonucleic Acid
Myg	myoglobin

NAFLD	Non-alcoholic Fatty Liver Disease
NPY	Neuropeptide Y
NSTEMI	Non—ST-segment Elevation Myocardial Infarction
NT-proBNP	N-terminal proBNP
Ox-LDL	oxidized low-density lipoprotein
PAI-1	Plasminogen Activator Inhibitor-1
PAPP-A	pregnancy-associated plasma protein-A
PCI	Percutaneous Coronary Intervention
Pea3	Polyomavirus Enhancer Activator 3
PGC-1α	Peroxisome Proliferator-Activated Receptor Co-Activator Protein 1 α (that controls the expression of gluconeogenic genes)
PI3K	Phosphoinositol-3-kinase
PlGF	placental growth factor
PIP2	Phosphatidylinositol-4, 5-diphospate
PLC γ	Phospholipase Cγ
PPARα (PPARA)	Peroxisome Proliferator-Activated Receptor α
PPARγ (PPARG)	Peroxisome Proliferator-Activated Receptor γ
PTCA	Percutaneous Transluminal Coronary aAngioplasty
RAF	Rapidly Accelerated Fibrosarcoma (protooncogene cytoplasmic serine/threonine protein kinases of the Ras/Mos family)
RAS	Rat Sarcoma (an oncogene discovered in the retroviruses Harvey and Kirsten rat sarcoma viruses)

RNAi	Ribonucleic Acid interference
RXR	Retinoid X Receptor
sCD40L	Soluble CD40 Ligand
SBP	Systolic blood pressure
SEF	SL3-3 enhancer factor
SH2	Src homology 2
SirT1	Silent mating type Information Regulation 2 homolog 1
SOS	Son Of Sevenless
SPRY	Sprouty family of proteins (Receptor tyrosine kinase signaling modulators)
Src protein	Sarcoma (A PROTEIN-TYROSINE KINASE originally identified by homology to the Rous sarcoma virus)
STAT	Signal Transducer and Activator of Transcription
STAT5	Signal Transducer and Activator of Sranscription 5
STEMI	ST-segment Elevation Myocardial Infarction
TAG	Triacylglycerol
TF	Tissue Factor
TK	Tyrosine Kinase
TM	Transmembrane
TNF	Tumor Necrosis Factor
TNI	Troponin I
TNT	Troponin T
tPA	Tissue type Plasminogen Activator
Tyr	Tyrosine

TZDs	Thiazolidinediones
UA	Unstable Angina
VCAM	vascular cell adhesion molecule
VLCD	Very Low Calorie Diet
VLDL	Very Low Density Lipoproteins
VWF	von Willebrand factor
WAT	white Adipose Tissue

Abstract

***Background*:** Fibroblast growth factor 21 (FGF21) is an emerging metabolic regulator. Circulating levels of FGF-21 are found in obese individuals and subjects with metabolic syndrome or type 2 diabetes and are closely associated with obesity and cardiovascular risk. However data are limited for advanced outcomes such as coronary heart disease (CHD). Previous studies of FGF21in CHD have been largely confounded by obesity and did not describe FGF21 level in CHD in terms of severity.

Aim of work: Investigating the associations between serum FGF-21 in CHD subjects strictly matched for BMI. It also investigated the possible association between serum FGF21 and the coronary angiographic findings in terms of number of coronary vessels affected. Associations between serum FGF21, in CHD individuals, with diabetes, hypertension, or both were also addressed.

Methods: Seventy patients were recruited from individuals admitted to the Critical Care Unit, for coronary angiography to assess CHD. Twelve (age, sex and body mass index (BMI) matched) apparently healthy individuals were also included in the present study. After coronary angiography the patients group were classified into: Sub-group (A***)***: Coronary Artery Disease patients without DM or hypertension; Sub-group (B): Coronary Artery Disease patients with DM and/or hypertension; Sub-group (C): Subjects showing normal angiography but suffering from DM and/ or hypertension. Also CHD patients were classified according to number of stenosed coronary vessels into 3 subgroups with 1, 2 and multi-vessel affection. Fasting serum levels of FGF21, glucose, insulin and lipid profile was estimated.

Results: The present results illustrated an increase in the median levels of serum FGF-21 in CHD patients versus the control group. A significant increase in the median levels of FGF-21 was detected in CHD patients with two vessel and multi-vessel affection compared to the control group and the one-vessel affecting group. Serum concentrations of FGF-21 were also increased in CHD subjects with diabetes or hypertension in

comparison to diabetic and hypertensive patients not suffering from CHD. There was a highly significant positive correlation between serum levels of FGF-21 and each of BMI ($r=0.7$, $p < 0.001$), SBP($r=0.63$, $p < 0.001$), and DBP ($r=0.67$, $p < 0.001$). A weakly significant positive correlation was also found between serum levels of FGF-21 and each of TAG ($r=0.223$, $p < 0.05$) and serum levels of LDL-c ($r=0.223$, $p < 0.05$). A weakly significant negative correlation was also found between serum levels of FGF-21 and serum levels of HDL-c ($r=0.23$, $p < 0.05$). Multi–variate logistic regression analysis revealed that the SBP was an independent risk factor for CHD. ROC curve analysis indicated that the optimum cut off value for plasma FGF 21 level in patients with CHD versus non CAD was 256 which gives 60% sensitivity and 63.64% specificity.

Conclusion: This study provides clinical evidence revealing that serum concentrations of FGF-21 are increased in CHD subjects with diabetes or hypertension in comparison to diabetic and hypertensive patients not suffering from CHD. Our data suggest that serum concentrations of FGF21 in humans are not related to insulin secretion, but rather to lipid metabolism. SBP appears to be strongly associated with serum FGF21 in CHD subjects. The consistent increase in FGF21 seen in human CHD patients and apparent significant difference between severity classified subgroups raises the intriguing possibility that FGF21 could be a biomarker for CHD and may be used to asses severity of CHD.

Key Words: **Serum Levels - Fibroblast Growth Factor-21 (FGF-21) - Coronary Heart Disease**