Potential Role of Insulin-Resistance in Development of Hepatocellular Carcinoma in CHC Patients

Thesis

Submitted for Partial Fulfillment of Master Degree
In Medicine

By

Khaled Mohamed Raafat
M.B.B.Ch.

Under Supervision of

Prof. Dr./ Khaled Hassan Hemida
Professor of Medicine
Faculty of Medicine - Ain Shams University

Dr./ Engy Yousry El-Sayed
Assistant Professor of Medicine
Faculty of Medicine - Ain Shams University

Dr./ Ahmed Mahmoud Abd El Aleem
Lecturer of Medicine
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2014

Acknowledgement

First of all, I want to thank **GOD** *for supporting me and guiding me throughout my life.*

I wish to express my deep appreciation and gratitude to ***Professor Dr. Khaled Hassan Hemida*** *Professor of Medicine Faculty of Medicine, Ain Shams University, for his academic supervision, guidance, constant encouragement and valuable advice, which was essential for the completion of this study.*

My sincere gratitude to ***Dr. Engy Yousry El-Sayed*** *Assistant Professor of Medicine, Faculty of Medicine, Ain Shams University, for her kind help , support , advice and precious time.*

My appreciation to ***Dr. Ahmed Mahmoud Abdel Aleem*** *Lecturer of Medicine Faculty of Medicine, Ain Shams University, for his kind help, support and his valuable advices.*

Last but not least I would like to express my deep thanks and gratitude to my family for supporting and pushing me forward all the time.

Contents

List of Abbreviations (Cont.)

SU	Sunitinib malate
SVR	Sustained virologic response
T2DM	Type 2 diabetes mellitus
TACE	Transarterial chemoembolization
TAE	Transarterial (bland) embolization
TAG-72	Tumor-associated glycoprotein 72
TARE	Trans Arterial Radioembolization
TGF-β1	Transforming growth factor-β1
TNF-α	Tumor Necrosis Factor -a
TNM	Tumor, node, metastasis
US	Ultrasonography
VEGF	Vascular endothelial growth factor
VEGF	Vascular endothelial growth factor
Vil1	Villin1
VIP	Vaso-active intestinal polypeptide
VLDL	Very low density lipoprotein
WAT	White adipose tissue
ZAG	Zinc-α2-glycoprotein

List of Abbreviations

AASLD	The American Association for the Study of Liver Diseases
AFP	Alpha-fetoprotein
AFP-L3	Lens culinaris agglutinin-reactive fraction of AFP
AFU	α-L-fucosidase
ALCPS	The advanced liver cancer prognostic system
APC	Annual percentage change
AT	Adipose Tissue
ATMs	Adipose tissue macrophages
ATP	Adenosine triphosphatase
BCLC	The Barcelona Clinic Liver Cancer
BMI	Body mass index
CEUS	Contrast-enhanced ultrasound
CHC	Chronic hepatitis C
CLIP	Cancer of the Liver Italian Program
CSPH	Clinically significant portal hypertension
CT	Computed tomography
CTGF	Connective tissue growth factor
CTL	Cytotoxic T lymphocytes
CTPM	The Clinical Trials Planning Meeting
CVD	Cardiovascular disease
DCP	Des-c carboxy prothrombin
DLK1	Delta like 1 homolog
DWI	Diffusion-weighted imaging
EASL	The European Association for the Study of the Liver
ESLD	End-Stage Liver Disease
ET-1	Peptide endothelin-1
FFAs	Free Fatty Acids
FNAC	Fine needle aspiration cytology

List of Abbreviations (Cont.)

FNH	Focal nodular hyperplasia
FPG	Fasting plasma glucose
FPI	Fasting plasma insulin
GLP	Glucagon-like peptide
GLUT4	Type four glucose receptors
GP73	Golgi protein 73
GPC3	Glypican-3
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	high density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HSP	Heat shock protein
HTA	Hepatoma-associated gene
HTERT	Human telomerase reverse transcriptase
HVPG	Hepatic venous pressure gradient
ICC	Intrahepatic cholangiocarcinoma
IGF	Insulin like growth factor
IKK-beta	Inhibitor of nuclear factor kappa-B kinase subunit beta
IL-18	Interleukin-18
IL-6	Interleukin -6
IL-6	Interlucin-6
ILP	Interstitial Laser Photocoagulation
IR	Insulin resistance
IRS	Insulin receptor substrate
JNK	C-Jun N-terminal kinase
JUPITER	Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin

List of Abbreviations (Cont.)

LDL	Low-density lipoproteins
LMF	Lipid mobilizing factor
MHC-I	Class I major histocompatibility complex
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NF-kappa-B	Nuclear factor kappa-light-chain-enhancer of activated B cells
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NK cells	Natural killer cells
NOD	New-onset diabetes
OD	Odd's ratio
PAI	Percutaneous Acetic Acid Injection
PCEA	Polyclonal carcino-embryonic antigen
PEI	Percutaneous Ethanol Injection
PI3K	Phosphoinositide-3-kinase
PIVKA-II	Prothrombin induced by vitamin K absence-II
PP2A	Protein phosphatase 2 A
PPARγ	Peroxisome proliferator-activated receptor γ
QUICK	Quantitative insulin sensitivity cheek index
RFA	Radiofrequency ablation
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SCCA	Serum squamous cell carcinoma antigen
sdLDL	Small dense low-density lipoprotein
SHARP	Sorafenib HCC Assessment Randomised Protocol
SIRT	Selective Internal Radiation Therapy
SOCS	Suppressor of cytokine signaling
STAT	Signal Transducers and Activators of Transcription

List of Tables

Page

List of Tables (Cont.)

Page

List of Figures

Page

List of Figures (Cont.)

Page

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide and, owing to changes in the prevalence of the two major risk factors, hepatitis B virus and hepatitis C virus, its overall incidence remains alarmingly high in the developing world and is steadily rising across most of the developed world**(*Yang, 2010*).** Early diagnosis remains the key to effective treatment and there have been recent advances in both the diagnosis and therapy of HCC, which have made important impacts on the disease ***(Jane et al., 2009).***

According to the World Health Organization, about 130–170 million people are chronically infected with the Hepatitis C virus, with more than 350,000 people dying from Hepatitis C-related liver diseases each year. About 75–85% of newly infected persons develop chronic infection and 60–70% of chronically infected people develop chronic liver disease; 5–20% develops cirrhosis, and 1–5% dies from cirrhosis or liver cancer (HCC). In 25% of liver cancer patients, the underlying cause is hepatitis C ***(WHO, 2013).***

HCC is a common cause of liver-related death among HCV-infected persons, developing predominantly in those with cirrhosis. Nevertheless, several studies have reported that HCC occurs in persons with bridging fibrosis without definite cirrhosis, although far less commonly; there are new insights

into HCV-related hepatocarcinogenesis ***(George et al., 2013 AND Mittal & El-Serag, 2013).***

Chronic HCV infection is associated with the development of hepatic steatosis and unique, virus-specific alterations in host metabolism leading to the development of IR (***Hung et al., 2009*****),** which is one of the gravest metabolic disturbances of human body, growing rapidly all over the world. It is an important marker of metabolic syndrome in general, and is an independent risk factor for its cardiovascular complications ***(Persico et al., 2009).***

Recently, the relationship between HCV genotype and insulin resistance has been revealed where HCV genotypes 1, 3 and 4(predominantly in Egypt) are associated with more severe insulin resistance **(*Duseja et al., 2009*).** IR in chronic HCV infection predicts faster progression diseases to fibrosis and cirrhosis, leading to liver failure and hepatocellular carcinoma (HCC) ***(Kiran et al., 2013).***

Epidemiological studies have demonstrated that diabetes mellitus (DM) is associated with a 2-4-fold increase in the risk of HCC, regardless of the presence of other major HCC risk factors (HBV, HCV, and alcoholic liver disease) ***(Chao-Hung et al., 2010)*****.** About 17% to 30% of patients who suffer cirrhosis may be clinically diabetic. Diabetes that develops as a complication of cirrhosis is known as "hepatogenous diabetes" (HD) ***(Serag et al., 2013)***.

AIM OF THE WORK

The aim of this work is to elucidate the potential role of insulin resistance (IR) in development of hepatocellular carcinoma in chronic HCV patients by assessing homeostatic model of insulin resistance (HOMA-IR).

HEPATOCELLULAR CARCINOMA IN CHRONIC HEPATITIS C VIRUS PATIENTS

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide and, owing to changes in the prevalence of the two major risk factors, hepatitis B virus and hepatitis C virus, its overall incidence remains alarmingly high in the developing world and is steadily rising across most of the developed world **(*Yang, 2010*).** Early diagnosis remains the key to effective treatment and there have been recent advances in both the diagnosis and therapy of HCC, which have made important impacts on the disease ***(Jane et al., 2009).***

According to the World Health Organization, about 130–170 million people are chronically infected with the Hepatitis C virus, with more than 350,000 people dying from Hepatitis C-related liver diseases each year. About 75–85 % of newly infected persons develop chronic infection and 60–70% of chronically infected people develop chronic liver disease; 5-20% develops cirrhosis, and 1–5% dies from cirrhosis or liver cancer (HCC). In 25% of liver cancer patients, the underlying cause is hepatitis C ***(WHO, 2013).***

HCC is a common cause of liver-related death among HCV-infected persons, developing predominantly in those with cirrhosis. Nevertheless, several studies have reported that HCC