The Relation between Plasma Adiponectin and Leptin Concentrations in Prediction of Steatosis in Chronic Hepatitis C Patients

Thesis

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بِسْمِ اللَّهِ الرّحمَنِ الرّحيمِ

(...رَبِّ أَوزِعنِي أَن أَشكُرَ نِعمَتَكَ الَّتِي أَنْعَمْتَ عَلَيَّ و عَلى والِدَيَّ

و أَنْ أَعْمَلَ صَالِحاً تَرْضَاهُ و أَدْخِلْنِي بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ)

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Rami Ezzat A. Elfattah

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List of Abbreviations

ACC	: Acyl CoA carboxylase
AKt	: Also known as Protein kinase B (PKB)
ALT	: Alanine transaminase
AOX	: Acyl CoA oxidase
APM	: Adipose most abundant gene transcript
APoB	: Apo-lipoprotein-B
AST	: Aspartate transaminase
BMI	: Body mass index
BT	: Breakthrough
CHC	: Chronic hepatitis C
CPT	: Carnitine palmitoyl transferase
DVR	: Delayed virological response
EC	: Endothelial cells
EDHS	: Egyptian demography health survey
EGP	: Endogenous glucose production
ER	: Endoplasmic reticulum
ERK	: Extracellularrelated kinases
EVR	: Early virological response
FFA	: Free fatty acids
G-CSF	: Granulocyte colony stimulating factor
GGT	: Gamma glutamyl transaminase
GPCRs	: G-Protein coupled receptors
HAI	: Histologic activity index
HBV	: Hepatitis B virus
HCC	: Hepatocellular carcinoma
HCV	: Hepatitis C virus
HMW	: High molecular weight
HOMA	: Homeostasis model assessment
HSCs	: Hepatic stellate cells
HSF	: Highly saturated fats
ICAM	: Intercellular adhesion molecule
IDEAL	: Incremental Decrease in Endpoints through Aggressive Lipid lowering
IFN	: Interferon
IGF	: Insulin like growth factor
IL	: Interleukin

List of Abbreviations *(Cont...)*

IR : Insulin resistance
LMW : Low molecular weight
LPV : Lipo-viro particles
MAPK : Mitogen-activated protein kinase
MLR : Mixed lymphocyte reaction
MMP : Matrix metalloproteins
MTHFR : Methyelene tetrahydrofolate reductase
MTP : Microsomal triglycerides transfer protein
NADPH : Nicotinamide adenine dinucleotide phosphate
NAFLD : Non alcoholic fatty liver disease
NASH : Non alcoholic steatohepatitis
NCR : Non colony region
NF : Neuro-fibromatosis
NR : Null response
NS : Non structural
Ob : Obesity
ObR : Leptin receptor
OR : Odds ratio
PI3K : Phosphatidyl inositol-3 kinase
PPAR : Peroxisome proliferators activated receptor
PR : Partial non-response
ROS : Reactive oxygen species
RVR : Rapid virological response
SOCS : Suppressor of cytokine signaling
SREBP : Sterol regulatory element binding protein
STAT : Signal transducer and activator of transcription
SVR : Sustained Virological response
TGF : Transforming growth factor
TIMP : Tissue inhibitor of metalloproteins
TNF : Tumor necrosis factor
VEGF : Vascular endothelial growth factor
VLA : Very late antigen
VLDL : Very low density lipoprotein
WAT : White adipose tissue

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Introduction

Steatosis is a common histological feature of hepatitis C virus (HCV) infection ***(Lonardo et al., 2004).***

The prevalence of steatosis in liver biopsy specimens from patients with chronic HCV infection has been reported at around 50% ***(Lonardo et al., 2004).***

Studies found a role for steatosis in the progression of chronic HCV ***(Hourigan et al., 1999, Adinolfi et al., 2001 and Lonardo et al., 2004).*** In addition, hepatic steatosis is an independent risk factor for hepatocarcinoma in patients with chronic HCV infection ***(Ohata et al., 2003).***

The pathogenesis of steatosis in patients with HCV is not well understood. HCV-related steatosis is not always virally related, and other factors may coexist. Steatosis is associated with risk factors for nonalcoholic steatohepatitis (NASH), particularly obesity, rather than with alcohol consumption ***(Monto et al., 2002).***

Obesity is a well-recognized risk factor for the development of steatosis and of fibrosis in HCV infected patients ***(Hourigan et al., 1999, Adinolfi et al., 2001, Monto et al., 2002 and Lonardo et al., 2004).*** Visceral fat distribution rather than body mass index (BMI) proved to be associated with HCV related steatosis ***(Adinolfi et al., 2001).***

The mechanisms by which accumulation and anatomic distribution of adipose tissue may be related to the development of steatosis and fibrosis are under intense investigation. Adipose tissue has traditionally been considered an energy

storage organ, but over the last decade, a new role has emerged for the adipose tissue as an endocrine organ ***(Ahima and Flier, 2000 and Kirshaw et al., 2004).***

Adipose tissues secrete a variety of hormones including adiponectin and leptin, which may contribute to the development of metabolic abnormalities ***(Ahima and Flier, 2000 and Kershaw et al., 2004).***

In addition, adipose tissue produces and secretes inflammatory cytokines, for example TNF- alpha and IL-6. There are few data on adipocytokines and liver function. There are some controversial data about the relationship between serum leptin levels and HCV-related steatosis ***(Giannini et al., 2000 and Romero-Gomez et al., 2003).***

Regarding adiponectin, its levels are associated in healthy humans with plasma concentrations of various liver function tests; however, there is no data about the secretion of adiponectin during hepatitis C infection ***(Lopez-Bermejo et al., 2004).***

Leptin protects against fatty liver directly by activation of adenosine monophosphate–activated protein kinase (AMPK) ***(Rabe et al., 2008)*** and also by lowering the expression of sterol regulatory element binding protein (SREBP)-1 ***(Kakuma T, et al., 2000).***

Although the deleterious association between obesity and HCV infection is well recognized, it has not been ascertained whether adipocytokines and, in particular, adiponectin & leptin may have a role in the development of steatosis in chronic hepatitis C.

Aim of the Work

The aim of our study is to investigate the role of adiponectin and leptin in HCV-related steatosis.

Hepatitis C Virus

The hepatitis C virus (HCV) is a major cause of chronic liver disease with an estimated 170 million people infected worldwide. The spectrum of severity of the liver disease associated with HCV varies widely from nonspecific, minimal inflammatory changes to cirrhosis and hepatocellular carcinoma ***(Seeff, 2002).***

The seroprevalance of HCV in Egypt in an unselected adult population; are up to 25% ***(Alter et al., 1999).*** The rate of progression of chronic hepatitis C is also variable, depending on many cofactors, mostly host-related, such as age, gender, alcohol consumption, over-weightness and co-infections ***(Marcellin, 2002 and Alberti, 2005)***.

Therefore, HCV is already a major challenge to health care services throughout the world, and is likely to become an even greater challenge during the next two decades ***(Deparment of Health, 2002).***

Virology:

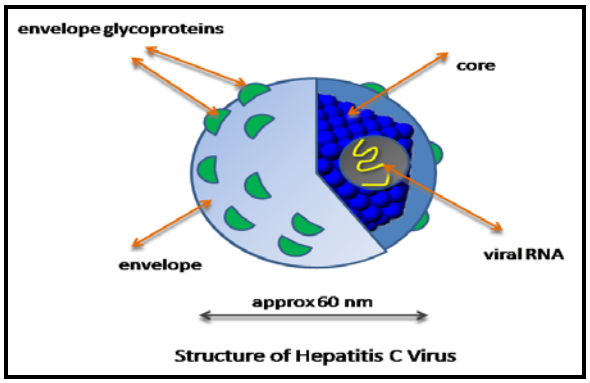

Figure (1): Image from WikiCommons

HCV is a small, enveloped RNA virus which has been allocated to a unique genus, designated Hepacivirus, within the family Flaviridae ***(Rosenberg, 2001)***. The HCV genome is a single stranded RNA molecule of positive polarity that contains a single open reading frame with the potential to encode a protein of c3000 amino acids in length ***(Rosenberg, 2001).***

The genomic organization and sequence of HCV resembles that of the pestiviruses and flaviviruses ***(Purcell, 1994, Lemon and Brown, 1995, Houghton, 1996 and Walker, 1999)***. The reservoir of HCV is man, but the virus has been transmitted experimentally to chimpanzees ***(Hsu and Greenberg, 1994).***

The HCV precursor proteins processed by host cell and virus proteases to yield ten structural and non-structural (NS) proteins. The genome of HCV is highly mutable. Because HCV is an RNA virus and lacks efficient proof reading ability as it replicates, virions infecting humans undergo evolution with time, giving rise to the HCV infection as a collection of different species. By constant mutation, HCV may be able to escape host immunologic detection and elimination ***(Hsu and Greenberg, 1994).***

The structural component of the virion is the core protein and envelope glycoprotein, E1 and E2. These proteins are cleaved from the precursor by host –cell peptidases. The 5non-coding regions [NCR] contain four highly conserved RNA domains and an internal ribosome entry site.