

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

## **Thesis**

Submitted for partial fulfillment of Master degree  
in Tropical Medicine

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2013**

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**بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ**

(...رَبِّ أَوْزَعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ  
الَّتِي أَنْعَمْتَ عَلَيَّ وَعَلَى وَالِدَيَّ  
وَأَنْ أَعْمَلَ صَالِحاً تَرْضَاهُ وَأَدْخِلْنِي  
بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ)

**صدق الله العظيم**

النمل.. آية رقم 19



## Acknowledgement

*First and foremost I thank Allah, the most merciful.*

*I wish to express my deep gratitude to **Prof. Dr. Zakarya Yahia Mahran**, Professor and Head of department of Tropical Medicine, Faculty of medicine, Ain Shams University for giving me the honor to work under his supervision with his eminent guidance, constant support and encouragement.*

*I would like also to express my profound thanks to **Dr. Amal Tohamy Abd-Elmo'ez**, Assistant professor of Tropical Medicine, Faculty of Medicine, Ain Shams University for her sincere help and great assistance and co-operation.*

*I wish to thank **Prof. Dr. Hanaa Ahmed Aly Amer**, Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University for her great help in practical work.*

*Finally, I wish to thank my family that supported me all the way till I finished this work.*

**Rami Ezzat A. Elfattah**

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## List of Abbreviations

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

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## **List of Abbreviations (Cont...)**

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

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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**

**T**he 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 (*Department of Health, 2002*).

### *Virology:*

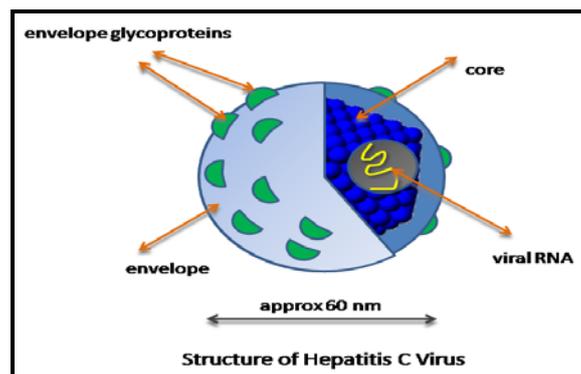


Figure (1): Image from WikiCommons



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.