# Evaluation of Serum Adiponectin Level in Patients with HCV Induced Chronic Liver Disease with and without Interferon Therapy

*Thesis*

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***By:***

**Shimaa Abdelaleem Mohamed Soliman**
M. B., B.Ch

## Supervised by

**Prof. Dr. Mohsen Moustafa Maher**
*Professor of Internal Medicine*
*Faculty of Medicine, Ain Shams University*

**Prof. Dr. Tarek Mohamed Yousef**
*Professor of Internal Medicine*
*Faculty of Medicine, Ain Shams University*

**Dr. Shereen Abou Baker Abdel-Rahman**
*Lecturer of Internal Medicine*
*Faculty of Medicine, Ain shams University*

**Faculty of Medicine**
**Ain Shams University**
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# Contents

List of Abbreviations ..... i

List of Tables ..... iii

List of Figures ..... v

**Introduction and Aim of the Work** ..... 1

**Review of Literature** .....

Hepatitis C Virus Infection ..... 4

Adiponectin ..... 72

Relation of adiponectin to HCV infection ..... 91

**Patients and Methods**..... 101

**Results** ..... 110

**Discussion**..... 128

**Summary** ..... 134

**Conclusion**..... 136

**Recommendations** ..... 137

**References** ..... 138

**Arabic Summary** ..... --

# List of Abbreviations

| | | |
|---|---|---|
| aa | : | Amino acid |
| ACC | : | Acyl coenzyme-A carboxylase |
| ADIPO-R1 | : | adiponectin receptor one |
| ADIPO-R2 | : | Adiponectin receptor two |
| AMP-K | : | AMP-activated kinase |
| AMPK | : | AMP-activated kinase |
| ARFP | : | Alternate reading fram protein |
| ASGP-R | : | Asialoglycoprotein receptor |
| BOC | : | Bociprevir |
| DAAs | : | Direct-acting antiviral agents |
| EDHS | : | Egyptian Demographic Health Survey |
| EGP | : | Endogenous glucose production |
| EIA | : | Enzyme immunoassay |
| EVR | : | Early virological response |
| FA | : | Fatty acid |
| FFA | : | Free fatty acid |
| G | : | HCV genotype |
| GBV-B | : | GB Virus B` |
| GBV-C | : | GB virus C |
| HAI | : | Histological activity index |
| HCV | : | Hepatitis c virus |
| HOMA2-IR | : | Homeostaisis model assessment of insulin resistance |
| HSC | : | Hepatic stellate cell |
| HSF | : | High-saturated fat |
| HSPG | : | Heparan sulfate proteoglycans |
| IDU | : | intravenous drug use |
| INF | : | Interferon |
| IR | : | Insulin resistance |
| IRES | : | Internal ripsome entery site |
| Kda | : | Kilo Dalton |
| LDL-R | : | Low density lipoprotein receptor |
| LEL | : | Large extracellular loop |

# List of Abbreviations (Cont.)

| | | |
|---|---|---|
| LPS | : | Lipopoysaccharide |
| NAFLD | : | Non alcoholic fatty liver disease |
| NASH | : | Non alcoholic steatohepatitis |
| Ns | : | Nonstructural protein |
| Nt | : | Neocliotides |
| ORF | : | Open reading frame |
| PCR | : | Polymerase chain reaction |
| PegINF | : | Peginterferon |
| Pis | : | Protease inhibitors |
| PPAR | : | Peroxisome proliferators activator receptor |
| RAVs | : | Resistance-associated variants |
| RBV | : | Rebavirin |
| RdRp | : | RNA-dependant RNA polymerase |
| SEL | : | Small extracellular loop |
| SOC | : | The standard of care for hcv treatment |
| SR-B1 | : | Scavenger receptor B type one |
| SVR | : | Sustained virologice response |
| TAPA-1 | : | Target of antiproliferative antibody -1 |
| TM | : | Transememberane regions from 1 to 4 |
| TNF | : | Tumor necrosis factor |
| TVR | : | Telaprevir |
| UTR | : | Untranselated reagion |
| WAT | : | White adipose tissue |

# List of tables


| *Table* | *Title* | *Page* |
|---|---|---|
| 1 | HCV proteins and their functions in the viral life cycle | 10 |
| 2 | Ishak modification for hepatic activity index (HAI) for scoring of necroinflammatory activity in chronic hepatitis | 32 |
| 3 | The conversion of FibroTest score into stages according to the most used histological classification (METAVIR score) for liver biopsies | 35 |
| 4 | Drug formulation of interferon | 45 |
| 5 | Child-Pugh score: Class A: 5-6 points; Class B: 7-9 points; Class C: 10-15 points | 67 |
| 6 | Shows description and comparison of different parameters of all patients in group I and group II | 111 |
| 7 | Showing descriptive and comparison between both groups as regard stages of liver fibrosis according to METAVIR score | 112 |
| 8 | Showing comparison between the different stages of liver fibrosis in group I as regard adiponectin level before INF therapy | 113 |
| 9 | Showing comparison between the stages of liver fibrosis in group I as regard adiponectin level after 12 weeks INF therapy | 114 |
| 10 | shows comparison between the adiponectin level before and after 12 weeks INF therapy in group I | 115 |

# List of tables (Cont.)


| *Table* | *Title* | *Page* |
|---|---|---|
| 11 | Shows the changes in adiponectin levels (increased-decreased) in responders and non responders to INF therapy in group I patients | 116 |
| 12 | Shows comparison as regard HCV RNA measured by PCR before and after 12 weeks INF therapy in group I | 117 |
| 13 | Showing a comparison between both groups as regard adiponectin levels before and after 12 weeks INF therapy | 118 |
| 14 | showing correlation between adiponectin level and other prameters in group I before INF therapy | 119 |
| 15 | Showing correlation between adiponectin level and other parameters in group I after 12 weeks INF therapy | 120 |
| 16 | Cut off value of adiponeetin levels for discriminating significant fibrosis (F > 2) from non significant fibrosis (F < 2) | 124 |
| 17 | Cut off value of adiponeetin levels for discriminating hepatic cirrhosis from other stages of hepatic fibrosis | 126 |

# List of Figures


| *Fig.* | *Title* | *Page* |
|---|---|---|
| 1 | HCV structure | 6 |
| 2 | Organization of HCV genome. NS: non structural | 7 |
| 3 | The structural organization of HCV genome | 9 |
| 4 | HCV genome organization (top) and polyprotein processing (bottom). The 5′ UTR consists of four highly structured domains and contains the IRES | 9 |
| 5 | HCV viral particle produced in a tissue culture system from a cloned viral genome | 17 |
| 6 | A simplified diagram of the HCV replication cycle | 17 |
| 7 | Hypothetical HCV replication cycle. HCV particles bind to the host cells *via* a specific interaction between the HCV envelope glycoproteins and cellular receptor | 18 |
| 8 | Interferon alpha/beta domain | 43 |
| 9 | Three vials filled with human leukocyte interferon | 43 |
| 10 | Different patterns of viral response during interferon-α-based therapy of chronic hepatitis C. SVR, sustained virological response | 57 |
| 11 | Liver cirrhosis as seen on an axial CT of the abdomen | 59 |
| 12 | Domains and structure of adiponectin | 74 |
| 13 | Correlations between blood adiponectin concentration and BMI in the healthy human population | 76 |

# List of Figures (Cont.)


| *Fig.* | *Title* | *Page* |
|---|---|---|
| 14 | Adiponectin action in the liver and skeletal muscle | 79 |
| 15 | Anti atherosclerotic effect of adiponectin | 80 |
| 16 | Effect of decreased adiponectin on the process of atherosclerosis | 81 |
| 17 | Summary of putative functions of adiponectin in protecting hepatocytes | 82 |
| 18 | A hypothetical model for the secretion and action of adiponectin | 87 |
| 19 | Shows comparison between both groups as regard stages of liver fibrosis according to METAVIR score | 112 |
| 20 | Showing correlation between adiponectin levels before INF therapy and liver fibrosis stages in group I | 113 |
| 21 | Showing comparison between the stages of liver fibrosis in group I as regard adiponectin level after 12 weeks INF therapy | 114 |
| 22 | Showing comparison between adiponectin levels before and after 12 weeks INF therapy in group I | 115 |
| 23 | Shows the changes in adiponectin levels (increased-decreased) in responders and non responders to INF therapy in group I patients | 116 |
| 24 | Showing comparison as regard HCV RNA measured by PCR before and after 12 weeks INF therapy in group I | 117 |
| 25 | Showing comparison between both groups as regard adiponectin levels after 12 weeks INF therapy | 118 |

# List of Figures (Cont.)


| *Fig.* | *Title* | *Page* |
|---|---|---|
| 26 | Positive correlation between adiponectin level before INF therapy and white blood cell count in group I | 121 |
| 27 | Positive correlation between adiponectin level before INF therapy and monocyte cells level in group I | 121 |
| 28 | Positive correlation between adiponectin level after12 weeks INF therapy and prothrombin time in group I | 122 |
| 29 | Positive correlation between adiponectin level after12 weeks INF therapy and INR in group I | 122 |
| 30 | Negative correlation between adiponectin level after 12 weeks INF therapy and spleen size in group I | 123 |
| 31 | Negative correlation between adiponectin level after 12 weeks INFtherapy and HCV RNA in group I | 123 |
| 32 | ROC curve analysis showing the diagnostic performance of adiponectin for discriminating patients with significant fibrosis (F > 2) from those with non significant fibrosis (F < 2). | 124 |
| 33 | showing cut off value of ROC curve analysis | 125 |
| 34 | ROC curve analysis showing the diagnostic performance of adiponectin for discriminating patients with hepatics cirrhosis from those with other stages of hepatic fibrosis | 126 |
| 35 | showing cut off value of ROC curve analysis | 127 |

# Introduction

Adiponectin is a protein hormone called adipocytokine produced and secreted by adipoeyte, with anti-diabetic, anti-lipogenic, anti-atherogenic, anti-inflammatory, and insulin sensitizing actions ***(Berg AH et al., 2001)***. Adiponectin directly affects inflammatory response by regulating both the production and activity of cytokines ***(Ouchi N et al., 2000).***

Concentration of total adiponectin in the blood is about 3-30mg/ml ***(Wouters et al., 2006)***. Low plasma levels of adiponectin are associated with insulin resistance and altered lipid pattern ***(Roden et al., 2006).***

There are two adiponectin receptors (ADIPORl and ADIPOR2), which have been cloned. Liver expresses both receptor genes and has the highest expression of ADIPO-R2 among the organs ***(Chinetti G et al., 2004).***

Adiponectin correlate negatively with liver fat and hepatic insulin resistance in diabetic patients ***(Bajaj M et al., 2004)***. It modulates hepatic fat content, has anti-steatotic effect on the liver and reduces the plasma level of free fatty acid and their influx into the liver ***(Fain NJ et al., 2004)***. Adiponectin has an antiinflamatory effect that could protect the liver from the development of inflammation and cell injury ***(Ouchi N et al., 2000).***

Adiponectin level was found to be higher in inflammatory HCV infection ***(Jonsson JR et al, 2005)***. it may be due to reduced ADIPO-R2 receptor level in chronic HCV infection. The reduced ADIPO-R2 expression was confirmed by immunohistochemistry ***(Corbetta et al., 2011)***. It is suggested that elevated levels of adiponectin in hepatic fibrosis may be due to adiponectin resistance in chronic HCV infection ***(Corbetta et al., 2011)***. Chronic HCV infected hepatocytes showed reduced ADIPO-R2 expression suggesting a pattern of adiponectin resistance ***(Corbetta et al, 2011)***.

The increased levels of adiponectin in liver cirrhosis may not dependent on the aetiology of liver cirrhosis, but depend on the clinical stage of chronic liver disease, and the

high adiponectin levels in chronic liver disease might at least partially be due to the proinflammatory state and could reflect one of the body's antiinflammatory mechanisms in these disorders ***(Tiege UJ et al., 2004).***

A trial to evaluate whether suppression of hepatitis C is associated with improvement in IR (insulin resistance) was done. Patients included in that trial underwent 24 weeks of pegylated interferon and ribavirm therapy and were categorized into HCV clearance groups at week 20 on the basis of HCV RNA levels; null responders had <1 logic decline, partial responders had >1 logic decline but detectable HCV RNA, and complete responders had no detectable HCV RNA. Change in IR by using the homeostasis model assessment (HOMA2-IR) was found ***(Aymin et al., 2010)***.

Association between HCV clearance and improvement in HOMA24R was found in that study. Multiple factors have been accounted for these improvements. Adiponectin, tumor necrosis factor-alpha, age, gender, ethnicity, body mass index, duration of infection, medications used, and fibrosis were all suggested ***(Aymin et al., 2010).***

In another study, treatment of chronic HCV patient with IFN-a resulted in a decrease of serum adiponectin levels but an improvement of insulin resistance in responders to the treatment ***(Jin et al., 2005).***

Serum adiponectin appears to be an independent predictor of liver steatosis in patients infected by HCV. It also appears to be an independent predictor for the achievement of end-of-treatment virological response after interferon alpha therapy ***(Theodores and Zografos et al., 2008).***

# Aim of the Work

To evaluate the serum levels of Adiponectin in patients with HCV causes chronic hepatitis, assess its levels in those patients with and without interferon therapy and detect its level before and during treatment n responders.

# Chapter1

## Hepatitis C Virus Infection

Hepatitis C is an infectious disease affecting primarily the liver, caused by the hepatitis C virus (HCV). The infection is often asymptomatic, but chronic infection can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years. In some cases, those with cirrhosis will go on to develop liver failure, liver cancer or life-threatening esophageal and gastric varices ***(Ryan et al., 2004).***

### HCV VIrology

The hepatitis C virus (HCV) is a small, enveloped, single-stranded, positive-sense RNA virus ***(Rosen, 2011)***. It is a member of the hepacivirus genus in the family Flaviviridae ***(Ray et al., 2009)***. There are seven major genotypes of HCV, which are indicated numerically from one to seven ***(Louie et al., 2011).***

### HCV genotypes

An important variable for all patients with chronic hepatitis C virus (HCV) is the "genotype" of HCV with which they are infected. This is the strain of the virus to which they were exposed when they were infected, and it is determined by a simple blood test.

Genotypes of HCV are genetically distinct groups of the virus that have arisen during its evolution ***(Bukh et al., 1995).***

Approximately 75% of Americans with HCV have genotype 1 of the virus (subtypes 1a or 1b), and 20-25% have genotypes 2 or 3, with small numbers of patients infected with genotypes 4, 5, or 6 ***(McHutchison et al., 1998)***. Most patients with HCV are found to have only one principal genotype,