



**IMPACT OF DIRECTLY ACTING ANTIVIRALS THERAPY
ON SERUM LEPTIN LEVEL IN EGYPTIAN PATIENTS
WITH CHRONIC HEPATITIS C INFECTION IN
CORRELATION WITH FIBROSCAN AS A MARKER OF
HEPATIC FIBROSIS**

Thesis

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**مستوى الليبتين فى الدم تأثير العلاج المباشر المضاد للفيروسات على
فى المرضى المصريين المصابين بالالتهاب الكبدى المزمن الفيروسي سى
بالارتباط مع فيروس سكان كدالة للتليف الكبدى**

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قالوا

لَسْبَحَانَكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

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CONTENTS

Subjects	Page
• List of Abbreviations	I
• List of tables	III
• List of Figures	V
• Introduction	1
• Review of literature:	
Chapter 1: Hepatitis C Virus	5
Chapter 2: Directly Acting Antivirals(DAAs)	21
Chapter 3: Leptin.....	55
Chapter 4: Leptin and hepatic fibrosis	69
• Aim of the Work.....	84
• Patients And Methods.....	85
• Results.....	92
• Discussion.....	114
• Summary	122
• Conclusion	124
• Recommendations	125
• References	126
• Arabic Summary	-

LIST OF ABBREVIATIONS

Abb.	Full term
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apoE	Apolipoprotein E
CDC	Center for Disease Control and prevention
CHC	Chronic viral hepatitis c
cLDs	Cytoplasmic lipid droplets
GT	Genotype.
HBV	Hepatitis B virus.
HCC	Hepatocellular carcinoma.
HCV	Hepatitis c virus.
HIV	Human immune deficiency virus.
HSC	Hepatic stellate cells.
IFN	Interferone.
IR	Insulin resistance.
JAK	Janus activation kinase.
Kpa	Kilo pascal.
LDL	Low density lipoprotein.
LVP	Lipovirparticles.
MMP	Matrix metalloproteinase.
MRI	Magnetic resonance image.
NANBH	Non A non B hepatitis.
NS	Non-structural.
OCLN	Occludin.
PAMPs	Pathogen associated molecular patterns.
PDGF	Platelet driven growth factor.

List of Abbreviations

PI	Protease Inhibitor.
PPAR	Peroxisome proliferator activated receptor.
RIG-1	Retinoic acid inducible gene-1.
RNA	Ribonucleic acid.
SVR	Sustained virological response
TGF-B	Transforming growth factor beta.
TIMP	Tissue metalloproteinase.
TNF	Tumor necrosis factor.
TRIF	TIR domain containing adaptor inducing IFN- beta.
U/S	Ultrasound.
UTRs	Untranslated regions.
VLDL	Very low density lipoprotein.

LIST OF TABLES

<i>Tab. No.</i>	<i>Subject</i>	<i>Page</i>
Table (1)	HCV DAAs approved in Europe in 2018	43
Table (2)	IFN-free, ribavirin-free combination treatment regimens available for treatment naïve patients and treatment experienced	44
Table (3)	Treatment recommendations for patients with chronic hepatitis C without cirrhosis	46
Table (4)	Leptin-deficient states.	65
Table (5)	Major Adipocytokines and Current Relevance to Hepatic Fibrosis	75
Table (6)	Major Functions of Key Adipocytokines involved in Hepatic Fibrosis	75
Table (7)	Characteristics of studied subjects with regard to gender	93
Table (8)	Characteristics of studied subjects with regard to age	94
Table (9)	Characteristics of studied subjects with regard to body mass index	95
Table (10)	Characteristics of studied subjects with regard to the regimen of Direct Acting Antiviral treatment employed	95
Table (11)	Characteristics of studied subjects with regard to the the degree of fibrosis by fibroscan before and 12 weeks post treatment.	96
Table (12)	Characteristics of studied subjects with regard to spleen size, liver size, PV diameter among cases and control	97
Table (13)	Characteristics of studied subjects as regards liver function tests among cases and control	97
Table (14)	Characteristics of studied subjects with regard to complete blood picture among cases and control	98
Table (15)	Characteristics of studied subjects with regard to leptin level among cases and control.	98
Table (16)	Characteristics of studied subjects with regard to lipid profile among cases and control	99
Table (17)	Characteristics of studied subjects with regard to CBC before and after treatment	100

List of Table

<i>Tab. No.</i>	<i>Subject</i>	<i>Page</i>
Table (18)	Characteristics of studied subjects with regard to INR , AST , ALT , T.Bilirubin , ALB before and after treatment	100
Table (19)	Characteristics of studied subjects with regard to LEPTIN level before and after treatment	101
Table (20)	Characteristics of studied subjects with regard to fibrosis stage by fibroscan before and after treatment.	103
Table (21)	Characteristics of the studied cases group with regard to leptin level variation with different treatment regimens before and after treatment	105
Table (22)	Characteristics of the studied cases group with regard to fibrosis degree variation with different treatment regimens before and after treatment	105
Table (23)	Correlation between baseline fibrosis stage and baseline leptin levels	106
Table (24)	Correlation between 12 weeks post treatment fibrosis stage and leptin levels	106
Table (25)	Correlation between baseline fibrosis stage and baseline leptin levels	107
Table (26)	Correlation between change of leptin levels post treatment in correlation with fibrosis stage	107
Table (27)	Correlation between different laboratory , , Age and abdominal US parameters before DAAs treatment and baseline leptin levels	108
Table (28)	Correlation between different laboratory , , Age and abdominal US parameters before DAAs treatment and baseline fibroscan stages.	109
Table (29)	Correlation between different parameters and leptin level 12 weeks after the end of treatment	110
Table (30)	Correlation between different parameters and fibroscan 12 weeks after the end of treatment	111
Table (31)	Regression analysis of Leptin with all other study variables.	112
Table (32)	Diagnostic performance of leptin in prediction of hepatic fibrosis stage 4 (advanced cirrhosis).	112

LIST OF FIGURES

<i>Fig. No.</i>	<i>Subject</i>	<i>Page</i>
Fig. (1)	Hepatitis C virus infection in the World. Analysis of seroprevalence	6
Fig. (2)	HCV life cycle and site of action of DAAs.	27
Fig. (3)	The central effects of leptin in states of energy excess and deficiency	59
Fig. (4)	(A) life cycle of the activated HSC, (B) life cycle of HSC	70
Fig. (5)	Interplay in signal transduction between leptin and adiponectin	72
Fig. (6)	Characteristics of studied subjects with regard to gender	73
Fig. (7)	Characteristics of studied subjects with regard to age.	94
Fig. (8)	Characteristics of studied subjects with regard to the regimen of Direct Acting Antiviral treatment employed	95
Fig. (9)	Characteristics of studied subjects with regard to the the degree of fibrosis by fibroscan before and 12 weeks post treatment.....	96
Fig. (10)	Characteristics of studied subjects with regard to leptin level among cases and control	98
Fig. (11)	Characteristics of studied subjects with regard to LEPTIN level before and after treatment.	101
Fig. (12)	Characteristics of studied subjects with regard to LEPTIN level before and after treatment	102
Fig. (13)	Characteristics of studied subjects with regard to fibrosis stage by fibroscan before and after treatment	103
Fig. (14)	Characteristics of studied subjects with regard to fibrosis stage by fibroscan before and after treatment	104
Fig. (15)	ROC-curve (Receiver Operating Characteristic-curve) illustrating the sensitivity and specificity of leptin assay in diagnosing hepatic fibrosis stage 4 in studied patients.	113

ABSTRACT

Background: Chronic viral hepatitis infection is associated with wide metabolic disarrangements. HCV interacts with lipid metabolism leading to steatosis, causing wide adipocytokines changes and impairs glucose metabolism leading to increased prevalence of insulin resistance (IR) and type 2 diabetes. This association is important, because several studies have shown that the presence of IR is associated with increased rates of fibrosis. And lower rates of rapid and sustained response to antiviral therapy.

Aims: The aim of this study is to evaluate the Impact of Direct Acting Antivirals. Therapy on serum leptin level in Egyptian patients with chronic hepatitis C infection in correlation with fibroscan as a marker of hepatic fibrosis.

Patients and methods: 50 subjects were divided into 2 groups: Group 1: 10 normal people (control group). Group 2: 40 patients with chronic hepatitis C virus infection treated with DAAs (Sofosbuvir & Daclatasvir \pm Ribavirin) for 3 months. All patients was subjected to leptin level measurement before and after treatment correlation with fibroscan in addition to measurement of leptin level in control group.

Results: leptin level among cases ranging from 50 to 140 pg/ml with mean (94.625 ± 23.132) while among control from 20 to 95 pg/ml with mean (56.600 ± 26.467) , unlike leptin level among the studied cases group before treatment ranging from 50 to 140 pg/dl with mean 94.625 ± 23.132 pg/ml while after treatment ranging from 50 to 135 pg/ml with mean (92.500 ± 25.013) .the mean difference between pretreatment and 12 weeks post treatment is 2.125 ± 16.008 pg/ml with p value of 0.406. fibrosis degree among the studied cases group before treatment ranging from 4.8 to 20.6 kPa with mean (10.348 ± 4.510) kPa while after treatment from 3 to 14.4 kPa with mean (7.875 ± 3.382) kPa). the mean difference between pretreatment and 12 weeks post treatment is 2.473 ± 1.870 kPa with P value of $<0.001^*$ denoting statistically significant difference as fibrosis degree markedly decreased after treatment with lower post treatment fibrosis stage in correlation to pretreatment stage. **Conclusion:** Serum leptin was found to be higher in chronic hepatitis c than normal person but there was no difference between pretreatment and post treatment level, in contrast to fibroscan which showed marked reduction of fibrosis degree after treatment with DAAs and SVR

Key word:

apoE: Apolipoprotein E, **HBV:** Hepatitis B virus, **Kpa:** Kilo pascal, **NANBH:** Non A non B hepatitis.

INTRODUCTION

Hepatitis C virus (HCV), a human pathogen responsible for acute and chronic liver disease, has variants classified into 7 major genotypes and infects an estimated 170 million individuals worldwide (*Chang et al., 2016*). It affects insulin signaling, and much of its life cycle is closely associated with lipid metabolism (*Chang 2016*). In addition to cirrhosis and hepatocellular carcinoma, HCV is thought to cause metabolic alterations, including steatosis, dyslipidemia, insulin resistance (IR), diabetes, obesity, and cardiovascular events (*Hu et al 2016*). Although most HCV infections are currently curable using potent direct-acting anti-viral agents, not all HCV-associated cardiometabolic complications are reversible after viral clearance (*Chang 2016*).

Adipose tissue has emerged as an important endocrine organ that exerts vital endocrine and immune functions via adipokines (*Chang et al., 2015*). Moreover, free fatty acids and glycerol derived from visceral adipose tissue reach the liver and stimulate the biosynthesis of lipoprotein and glucose, respectively (*Funahashi et al., 2007*). Because adipose tissues and the liver are functionally linked, elucidating the relationship between adipokine alterations and HCV infection has the potential to reveal the basis of HCV-associated cardiometabolic complications and probe the therapeutic targets. The adipokine leptin, a product of the obese gene, is primarily expressed in adipose tissue but

is also expressed in other organs, including the liver (*Ahima et al., 2000*).

Most of the circulating leptin originates from subcutaneous, but not visceral adipose tissue, which may reduce its biological activity (*Chang et al., 2015*). Leptin is crucial for maintaining total body fat and glucose homeostasis as well as regulating food intake and energy expenditure through a complex central feedback mechanism (*Kishimoto et al., 1994*). Its secretion is influenced by numerous physiological and hormonal factors. The leptin receptor is expressed in hypothalamic neurons, T cells, and hepatic stellate cells (*Saxena et al., 2002*). Importantly, leptin promotes IR to increase intracellular fatty acids in hepatocytes, amplifies proinflammatory responses (*Loffreda et al., 1998*), and mediates hepatic fibrogenesis during chronic liver injury (*Leclercq et al., 2002*) through the activation of hepatic stellate cells (*Ikejima et al., 2002*). Concordantly, leptin levels are elevated in patients with a higher fibrosis index (*Patel et al., 2003*).

Importantly, leptin is critical for the modulation of adaptive and innate immune responses, such as regulating T-cell-mediated immune responses (*Lord et al., 1998*) and natural killer cell activity (*Siegmund et al., 2002*), as well as increasing complement component 3 (C3) levels . Because both HCV infection and leptin are critically involved in metabolism, inflammation, and immunity, their

potential relationship has attracted attention; however, no definite conclusion regarding such a relationship has been drawn (*Nestvold et al., 2015*).

Serum leptin levels have been found higher in patients with chronic hepatitis C (CHC) and particular in those with more severe fibrosis or cirrhosis (*Bolukbas et al., 2004*); however the results are conflicting (*Ben-Ari et al., 2002*). Leptin has been also implicated in many actions including liver fibrogenesis (*Bethanis et al., 2006*). Recent observations in patients with CHC indicate that liver steatosis and insulin resistance has been associated with progressive hepatic fibrosis and sustained virologic response (SVR) to antiviral treatment (*Charlton et al., 2006*).

It is known that serum leptin regulates insulin secretion and tissue responsiveness to this hormone (*Cohen et al., 1996*). Leptin is an adipokine that contributes to the pathogenesis of liver steatosis (*Saxena et al., 2002*). In patients with CHC, higher serum leptin concentrations have been associated with the presence of steatosis (*Romero-Gómez et al., 2003*). a recent study reported that high serum leptin concentrations is correlated with more severe steatosis, lower viremia, and a lower antiviral response, mainly in patients infected with HCV genotype-1, which constituted 71% of the study population (*Eguchi, Mizuta et al., 2006*).

Leptin plays an important role in the regulation and metabolism of body fat and may induce insulin resistance, increase fatty acid concentrations in the liver, and enhance lipid peroxidation (*Adinolfi et al., 2001*). Leptin may act as an immunomodulator, inducing the release of cytokines, such as tumor necrosis factor (TNF)- α , interferon (INF)- γ , interleukin (IL)-18, and transforming growth factor (TGF)- β 1, thus promoting liver steatosis and fibrosis (*Giannini et al., 2001*).