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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Contents

List of Abbreviations

Abb.	Full term

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..... Lipoviroparticles.

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 drived growth factor.

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.

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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 ± Ribavirin) for 3 months. All patients was subjected to leptin level measurement before and after treatment correlation with fibroscanin 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±4.510kPa) 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 tofibroscan 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)-β1, thus promoting liver steatosis and fibrosis ***(Giannini et al., 2001)***.