Study the Effect of Sofosbuvir Plus Daclatasvir on Lipid Metabolism and Apolipoprotein B in Chronic Egyptian Hepatitis C Virus Patients

Thesis

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List of Abbreviation

APOS	Apolipoprotiens
DAA	Directly acting anti viral
END	End of treatment
GT	Genotype
HBA1C	Hemoglobin A1C
HCV	Hepatitis c virus
HDL	High density lipoprotein
Hg	Hemoglobin
INF	Interferon
IR	Insulin resistance
LDL	Low density lipoprotein
SOF	Sofosbuvir
SVR	Sustained virologic response
T.CH	Total cholesterol
TG	Triglyceride
VLDL	Very –low density lipoprotein
WBCS	White blood cell

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ABSTRACT

Background: HCV, a member of the Flaviviridae family, infects persistently approximately 185 million persons globally. Chronic hepatitis C predisposes sufferers to the development of liver cirrhosis, hepatocellular carcinoma, as well as metabolic disorders and cardiovascular diseases. **Aim of the work:** The aim of this study is to demonstrate the effect of direct acting antiviral drugs (sofosbuvir and daclatasvir) on lipid profile and Apolipoprotien B in Chronic hepatitis C patients. The study included two groups with Comparable age, sex and body mass index (BMI). **Patients and Methods:** This prospective study was carried out in the Gastroenterology and Hepatology clinics at Ain Shams University Hospitals in the period between January 2018 and July 2018. The study was conducted on two groups with comparable age, sex and body mass index (BMI). Group 1 include 40 CHC patients receiving sofosbuvir and daclatasvir in dose of 400mg once daily and 60mg once daily respectively for 12 weeks. Group 2 40 completely healthy individuals as a control Patients with HBV or HIV, diabetic patient, patient on statin therapy or drinking alcohol are excluded from the study. **Results:** The study has demonstrated 100% negative PCR for HCV at the end of therapy indicating high efficacy of DAA in treatment of chronic hepatitis c virus patients. We found that Patients in the HCV Group had lower total cholesterol levels, LDL cholesterol, HDL cholesterol, triglyceride and apolipoprotien B than the uninfected control group. The study show significant increase in serum triglyceride (p value 0.001) and HDL cholesterol (P value 0.044) immediately after the end treatment. And non-significant increase in total cholesterol and LDL cholesterol after treatment than at base line indicating direct effect of HCV clearance on host lipid metabolism. The study also demonstrate significant increase in serum Apolipoprotien B (p value <0.001) with the end of treatment. These findings suggest that HCV infection by itself may be involved in the disturbance of serum lipoproteins/ apolipoproteins Therefore, examining serum lipoproteins/apolipoproteins is beneficial for monitoring disturbed lipid metabolism induced by HCV. **Conclusion:** The sofosbuvir/daclatasvir -based therapy continues to show a high degree of effectiveness in the treatment of CHC GT4. High efficacy of these drugs ameliorates the predictive effect of metabolic factors. The lipid changes in this study were interesting, in our study, the changes in lipid profile after DAAs were atherogenic, which might represent a predictor for cardiovascular risk. This may justify long-term monitoring of lipid parameters.

Keywords: Sofosbuvir Plus Declatasvir, Lipid Metabolism, Apolipoprotein B, Hepatitis C Virus

INTRODUCTION

HCV, a member of the *Flaviviridae* family, infects persistently approximately 185 million persons globally. Chronic hepatitis C predisposes sufferers to the development of liver cirrhosis, hepatocellular carcinoma, as well as metabolic disorders and cardiovascular diseases **(Brandã et al, 2018)**.

Chronic HCV infection disturbs lipid metabolism, including hypocholesterolemia and hypobetalipoproteinemia **(Felmlee et al, 2013)**. HCV infection and replication are known to rely on host lipid metabolisms. Briefly, HCV virion form complexes with triglyceride-rich lipoproteins known as lipoviral particles (LVPs), including very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL), which circulate in the bloodstream **(Chida et al, 2018)**. HCV-LVPs enter hepatocytes from LDL receptors via multiple steps, including attachment with CD81, scavenger receptor class B type 1 (SR-B1), claudin-1, and occludin. HCV activates sterol regulatory element binding proteins, which regulate cholesterol and fatty acid biosynthesis**,** **(Waris et al, 2007)** and reduce β-oxidation by downregulating peroxisome proliferation-activated receptor α9, 10 to enhance lipid biogenesis for replication of HCV in hepatocytes. HCV also reduces VLDL secretion from

hepatocytes by inhibiting microsomal triglyceride transfer protein activity **(Chida et al, 2018)**. In addition, several apolipoproteins are crucial for HCV-LVPs formation **(Fukuhara et al, 2015)** and entry into hepatocytes. HCV infection is strongly associated with characteristic apolipoprotein levels **(Aizawa et al, 2015).**

The proteins associated with lipoproteins, known as apolipoproteins (apos), are required for the assembly, structure, and function of lipoproteins, and apos activate enzymes important in lipoprotein metabolism. It is known that apo-B is the major structural protein in chylomicron, Very Low Density Lipoprotein (VLDL)- Cho, Intermediate Density Lipoprotein (IDL)-Cho and Low Density Lipoprotein (LDL)-Cho, which are synthesized in the liver **(Kogame et al , 2012).**

The impairment of lipid metabolism may contribute to the rapid progression of liver disease and unfavorable therapeutic outcomes in patients with chronic hepatitis C **(Brandão et al, 2018).**

Interferon (IFN)-based therapy was the most common form of treatment for chronic HCV infection for more than two decades. Triple therapy with pegylated-IFN, ribavirin (RBV), and HCV protease inhibitors achieved high rates of overall sustained virological response (SVR) in patients

infected with HCV genotype 1 **(Hayashi et al , 2014).** Successful IFN-based therapy for chronic HCV infection was shown to improve liver function, and to reduce the incidence of HCC and liver-related mortality **(van der Meer et al , 2012)** Furthermore, posttreatment increases in serum total and LDL-cholesterol levels were observed in HCV patients with SVR **(Corey et al , 2009).** However, studies with IFN-based therapy were limited in terms of evaluating dynamic changes in serum biochemical parameters of lipid metabolism during treatment, as administration of exogenous IFN-α in the setting of treatment for chronic HCV infection and other conditions can reduce LDL-cholesterol levels and raise triglyceride levels **(NCHEZ-CHAPARRO et al, 2000).**

Treatment for chronic HCV infection is rapidly evolving from IFN-based to IFN-free therapy consisting of direct acting antivirals (DAAs). Combination therapy with daclatasvir (DCV) and asunaprevir (ASV) has been approved as the first IFN-free regimen, with oral combinations of DAAs used for patients infected with HCV genotype 1 in Japan **(Kumada et al, 2014)**. Direct acting antivirals become the main line for treatment of hcv in Egypt, However, the effects of DAAs on the risks of developing HCC, liver-related mortality, and extrahepatic manifestations, including disturbed lipid metabolism, have not been fully clarified.

AIM OF THE WORK

Study the effect of treatment of hepatitis C virus with sofosubovir and daclatasavir on lipid and apolipoprotein B in patients with chronic hepatitis C.

HEPATITIS C INFECTION

Hepatitis c virus infection, and its long-term resultant consequences, is a major endemic medical health problem in Egypt. With the highest prevalence rate in the world. It is widely accepted that the implementation of mass population antischistosomal Treatment involving administration of tartar emetic injections (from 1950s to 1980s) led to widespread infection. What is less well known, however, is that these schemes were implemented by the Egyptian Ministry of Health on the advice of the World Health Organization. There has been a spectrum of treatments to target the public health disaster represented by the hepatitis C problem in Egypt: from the use of PEGylated interferon to the recent use of direct some new treatments have shown >90% efficacy. However, cost is a Key barrier to access these new medicines. This is coupled with a growing population, limited resources, and a lack of infection control practices which means Egypt still faces significant disease control issues today **(Elgharably et al, 2017)**

What is HCV?

HCV is a hepatotoxic RNA virus of the genus Hepacivirus in the Flaviviridae family. The virus exists as an enveloped, Positive-stranded RNA virus which Is ~50 nm in

size. (Figure: 1). The HCV RNA strand is made up of ~9600 Nucleotide bases and is covered by an icosahedral nucleocapsid which is further surrounded by A lipid bilayer and glycoproteins. HCV is grouped into 6 major genotypes that exhibit at least 30% variation in nucleotide sequence from One another. This genetic variation within the population is a powerful selection mechanism for resistance to both Medicinal drugs and evasion of the immune system. Most common HCV RNA genotype in Egypt is genotype 4, Representing >85% of all HCV cases in Egypt **(Kim et al, 2013).**

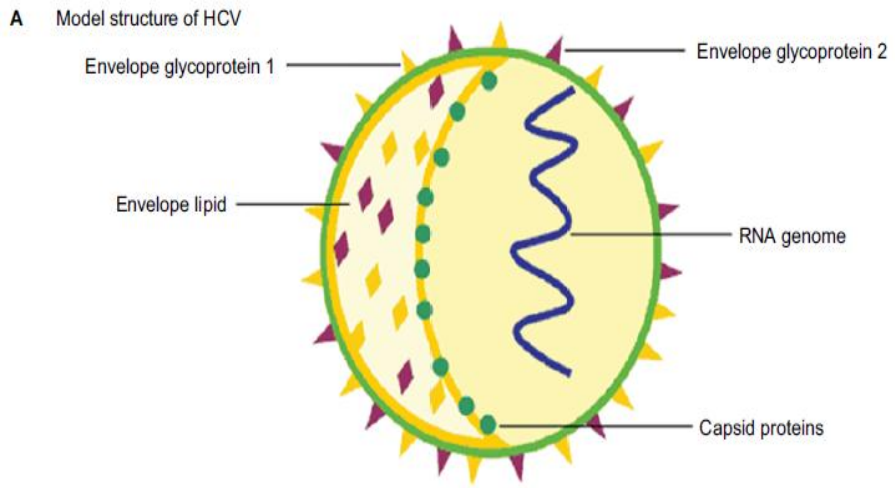

Fig. (1) Model structure of HCV

(Elgharably et al, 2017)

Prevalence

Egypt has the highest prevalence of hepatitis C virus (HCV) in the world, estimated nationally at 14.7% **(Blach et al, 2017)**. This nation has weathered the largest iatrogenic transmission epidemic of blood-borne pathogens in human history during the era of parenteral antischistosomal therapy (PAT). Numerous HCV prevalence studies have published various estimates from different Egyptian communities, suggesting that Egypt, relative to the other nations of the world, might be experiencing intense ongoing HCV transmission **(Mohamoud et al, 2012)**. Since then, it became apparent that HCV infection was widespread among Egyptians and that it was the main cause of liver disease in the country.

The Demographic Health Survey (DHS) of 2008 showed a national prevalence of 14.7% among those aged between 15 and 59 years, which increased with age and was higher in males than in females in all age groups studied. A mathematical model was used to estimate the 2014 prevalence. Assuming that 65,000 patients were treated annually with pegylated (PEG) interferon and ribavirin (RBV)) with a sustained virologic response (SVR) rate of ~50%, that) 32,000 patients were cured, that an estimated 150,000 new) infections occur annually leading to 100,000 chronic HCV) infections and that 150,000 persons with HCV