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Study of risk factors in patient with persistent elevation of liver enzymes after treatment of chronic HCV by Direct acting antiviral drugs

A Thesis

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By

Asmaa Abdelraouf Ghobashy

(M.B.B.CH)

Supervisors

Prof. Dr. Amira Ahmed salem

Professor of Internal medicine & Gastroenterology
Faculty of Medicine - Ain Shams University

Prof. Dr. Hisham hamdy Radwan

Professor of Internal medicine & Gastroenterology
Faculty of Medicine - Ain Shams University

A. Prof. Dr. Ayman gamil Anwar

Assistant Professor of Internal medicine & Gastroenterology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
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Asmaa Abdelraouf Ghobashy

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List of Abbreviations

Abb.	Full term
AFP	Alpha-fetoprotein
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
CRP	C-reactive protein
CT	Computed tomography
CVD	Cardiovascular disease
DAAS	Direct acting antiviral drugs
DNA	Deoxyribonucleic acid
FBS	Fasting blood sugar
GI	Gastrointestinal
Hb	Haemoglobin
HBV	Hepatitis B virus
HDL-c	High density lipoprotein cholesterol
IGT	Impaired glucose tolerance
INR	International normalized ratio
IV	Intravenous
LDL-c	Low density lipoprotein cholesterol
LFT	Liver function test
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
Plt	Platelets
PT	Prothrombin time
ROC-curve	Receiver Operating Characteristic-curve

List of Abbreviations Cont...

Abb.	Full term

SAAG ..... Serum albumin-ascites gradient
SVR ..... Sustained virological response
T2DM ..... Type two of diabetes mellitus
TG ..... Triglyceride
TNF-a ..... Tumor necrosis factor alpha
VLDL ..... Very low density lipoprotein
WBC ..... White blood cells

INTRODUCTION

Hepatitis C virus (HCV) infection is a major global health challenge; it is estimated that more than 80 million people are chronically infected worldwide, with 3- 4 million new infections and 350000 deaths occurring each year because of HCV- related complications. Egypt is the country with the highest HCV prevalence in the world **(Kandeel et al., 2017).**

Treatment of HCV infection has been revolutionized by the recent development of potent direct antiviral agents (DAAS). Interferon-free treatment with DAAs provides excellent chances for sustained HCV elimination and thus can prevent progression of liver disease. Use of interferons for HCV therapy has essentially ceased in all countries, where DAAS regimens are available **(Spengler, 2018).**

However, even with extremely high rates of sustained virological response (SVR), as seen with currently available regimens (>90% in most populations), the few patients with unsuccessful responses to therapy will need to be considered for retreatment **(AASLD-IDSA, 2015).**

However viral cure from hepatitis is not closely associated with resolution of liver disease Patients with advanced liver fibrosis or concomitant liver disease may

need clinical follow up and ongoing medical care after resolution of the hepatitis C infection **(Flisiak R, 2018).**

This has been demonstrated for persistent risk of hepatocellular carcinoma (HCC) development despite HCV eradication in patients with liver cirrhosis **(Roche B et al., 2018).**

More recently fatty liver due to metabolic syndrome or excessive alcohol consumption, has gained attention as a considerable and enduring comorbidity after SVR with DAA **(Noureddin M et al., 2018).**

Insulin resistance activates lipolysis resulting accumulation of non-esterified fatty acids. This enhanced fat accumulation in liver is known to be directly toxic to hepatocytes **(Judi L et al., 2010).**

This attributes increase in transaminases and diminished synthetic capacity of liver **(Harris EH, 2005).**

One of the hepatic manifestation of diabetes mellitus with metabolic syndrome is NAFLD and more specifically ALT has been used as a marker of NAFLD **(Westerbacka JCA, 2008).**

Chronic hyperinsulinemia and relative insulin resistance cause a cascade of reactions that lead to increase in lipogenesis and associated fatty changes. Accumulation of

free fatty acid is known to be toxic to hepatocytes cause disruption of cell membrane، mitochondrial dysfunction, oxidative stress and increase in proinflammatory cytokine – Tissue Necrotic Factor **(Agarawal J, 2015).**

Accumulation of intracellular glycogen in hepatocytes lead to liver injury showing typical biochemical findings of mild to moderate rise in ALT, AST **(Ahmed RM, 2015).**

AIM OF THE WORK

The aim of this study is to determine risk factors that cause persistent elevation of liver enzymes in hepatitis c virus patients treated by direct acting antiviral drugs .

Chapter One

HEPATITIS C VIRUS (HCV)

HCV is a member of the family Flaviviridae and the genus Hepaci virus. The HCV genome is a positive-stranded RNA, which encodes a core protein (C), two envelope glycoproteins (E1 and E2), and several non-structural proteins (NS1, NS2, NS3, NS4A, NS4B, NS5A and NS5B) (figure 1) **(Falcon et al., 2017).**

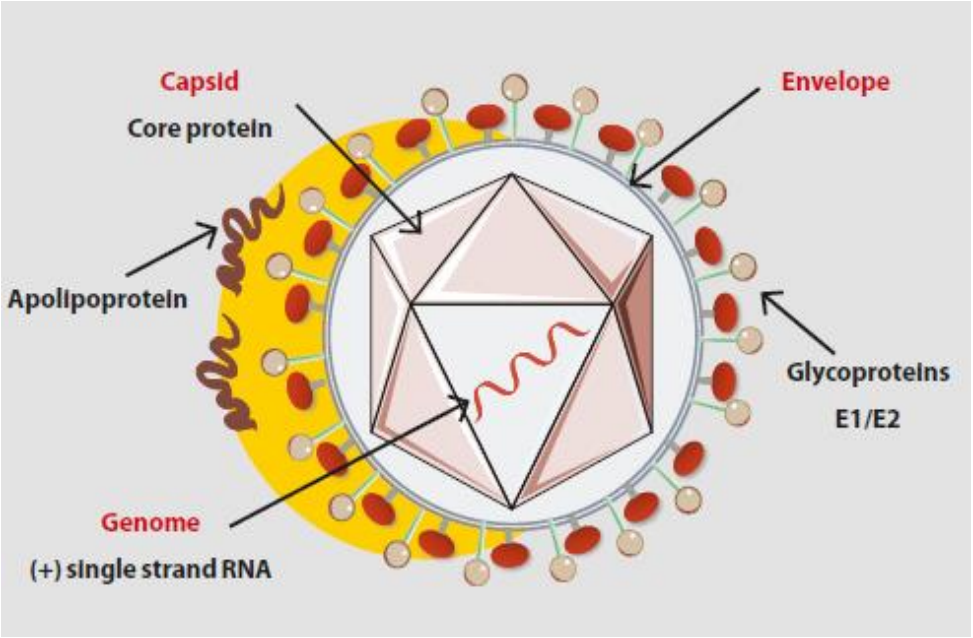

Figure 1: The structure of the hepatitis C virus lipoviro-particle **(Falcon et al., 2017).**

HCV genotypes & geographical distribution

Seven major genotypes have been recognized to date; the complete genomes of which differ from each other by at least 30% at the nucleotide level **(Borgia et al., 2018).**

Each genotype is further divided into a variable number of more closely related subtypes (currently more than 100 subtypes). The natural course of infection, pathogenesis, treatment regimens, treatment duration and outcomes largely depend on genotype (GT) and subtype of the infecting HCV strain. For examples, the rate of evolution to chronicity is higher in genotype 1b compared to other genotypes (92% versus 33–50%). Different transmission routes for HCV infection has shown to be associated with the genotype of the virus. Subtype 1b transmits effectively via blood transfusion, while subtypes 1a and 3a transmit predominantly through intravenous drug use **(Le Ngoc et al., 2019).**

In 2006, a novel HCV genotype was identified in a patient originating from the Democratic Republic of Congo, which was later classified as HCV GT7a with subsequent identification of GT7b. Genotype 1 is the most prevalent globally (46%) and predominates in Europe, North America, and Australia followed by GT3 (30%) primarily distributed

in South Asia, particularly the Indian sub-continent **(Gower et al., 2014)**.

Four patients previously classified as GT5 by line probe assay (LiPA) or Abbott Real Time PCR assays were identified as infected with a novel HCV genotype. This novel HCV genotype, GT8, is genetically distinct from previously identified HCV GT1-7 with >30% nucleotide sequence divergence to the established HCV subtypes. All four patients were originally from Punjab, India, but now reside in Canada and are epidemiologically unlinked **(Borgia et al., 2018)**.

Egypt has the highest prevalence of HCV worldwide **(Breban et al., 2013)** and the highest prevalence of HCV-GT4 **(Wantuck et al., 2014)**, HCV is responsible for almost 90% of infections and is considered a major cause of chronic hepatitis, liver cirrhosis, hepatocellular carcinoma, and liver transplantation **(Guerra et al., 2012)**.

HCV genotype 4 has been restricted to a few countries in the Middle East and Africa **(Salemovic et al., 2017).**

Previous epidemiological surveys tested whether people had antibodies against the virus, which is less precise and that 1.75 million new HCV infections occur each year. Once the chronic status is established, the disease progresses gradually. In approximately 10–20 % of patients with chronic