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The Role of Retinol Binding Protein 4 (RBP4) in Prediction of Response to New Direct Acting Antiviral Drugs (DAAS) in Chronic Hepatitis C

A Thesis

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Ibrahim Youssef Abdelwarth

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Abb.	Full term
AFP	Alpha-fetoprotein
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
CK	Creatine kinase
CRP	C-reactive protein
CT	Computed tomography
CVD	Cardiovascular disease
DAAS	Direct acting antiviral drugs
DHS	Demographic Health Survey
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
FBS	Fasting blood sugar
GI	Gastrointestinal
GLUT4	Glucose transporter 4
Hb	Haemoglobin
HBV	Hepatitis B virus
HDL-c	High density lipoprotein cholesterol
HOMA-IR	Homostasis model assessement of insulin resistance
Ig	Immunoglobulin
IGT	Impaired glucose tolerance
INR	International normalized ratio
IV	Intravenous
KBS	Kilopascal

List of Abbreviations Cont...

Abb.	Full term
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
RBP	Retinol binding protein
RBP4	Retinol binding protein 4
ROC-curve	Receiver Operating Characteristic-curve
RXR	Retinol x receptor
SAAG	Serum albumin-ascites gradient
SVR	Sustained virological response
T1DM	Type one of diabetes mellitus
TG	Triglyceride
TNF-a	Tumor necrosis factor alpha
VLDL	Very low density lipoprotein
WBC	White blood cells

Abstract

Background: Hepatitis C virus is global health burden and major health hazard in Egypt, Since the virus is the etiological factor of chronic hepatitis that frequently progress to a Cirrhosis and hepatocellular carcinoma (HCC).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.

Objective: To determine the value of RPB4in the prediction of response to new DAAS. Treatment in chronic HCV infected patients and to correlate its level with their catabolic Profile and fibrosis degree among chronic HCV

Patients and Methods: This study was Prospective cohort clinical study that was Conducted at hepatology and virology outpatient clinic at Ain Shams University Hospital & Hepatology and virology outpatient clinic at Kafr–Sheikh liver institute from January 2019 to October2019after informed consent.

Results: The present study showed that the best level of RBP4in prediction of hepatic Fibrosis stage4was≤46pg/ml and had sensitivity of 100% while the specificity was 66.67%.The positive predictive value was50% while the negative predictive value was100% and test accuracy was80.5%.

Conclusion: Serum RBP4 was found to be higher in chronic hepatitis C naïve patients than Normal person; there was significant reduction of RBP4 post treatment. Fibroscan showed Marked reduction of fibrosis degree after treatment with directly acting antiviral in both cirrhotic and non-cirrhotic patients regardless the treatment regimen used with improved. Over all liver function tests, liver enzymes and platelet count in patients who reached SVR And maintained negative PCR after treatment.

Keywords: HCV, DAAs, RBP4.

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)**.

As HCV patients are at risk for developing end-stage liver disease with a variety of complications including hepatocellular carcinoma and decompensated liver cirrhosis with the need for liver transplantation, chronic HCV infection is associated with an elevated risk for liver-related mortality **(Steinebrunner et al., 2015).**

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)**.

Retinol Binding Protein 4 (RBP4) is a protein that belongs to the lipocalin family **(van Dam and Hu, 2007).**

It is secreted mainly by hepatocytes (80%) and to lesser extent by adipose tissue (20%). It takes part in the control of metabolic and proliferative cell functions including steatogenesis by interacting with nuclear retinol X receptor (RXR)**(Desvergne, 2007).**

A pathogenic link was proposed between insulin resistance, diabetes and high serum and adipose levels of RBP4 **(Kloting et al., 2007).**

Its secretion from adipocytes is regulated by glucose transporter 4 (GLUT4) that mediates glucose uptake into muscle and fat cells. In insulin-resistant states the expression of GLUT4 is reduced in adipocytes resulting in decreased influx of glucose and increased secretion of RBP4**(Cengiz et al., 2010)**.

It was demonstrated that patients with chronic liver disease and more advanced fibrosis carried a significantly decreased RBP4 than controls, reflecting the impact of hepatic necro-inflammatory activity on RBP4**(Huang et al., 2009)**.

Iwasa et al. studied changes in RBP4 levels following interferon therapy. RBP4 levels were lower in chronic hepatitis C patients than controls concomitant with the grade of fibrosis, activity, and steatosis **(Iwasa et al., 2009)**.

A study made by **Petta et al.** had shown a remarkable association between the degree of hepatic steatosis and RBP4 levels, restricted to genotype1 hepatitis C patients and unrelated to abnormal metabolic features**(Petta et al., 2008)**.

AIM OF THE WORK

The aim of this study is to determine the value of RPB4 in the prediction of response to new DAAS treatment in chronic HCV infected patients and to correlate its level with the metabolic profile and fibrosis degree among chronic HCV

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).**

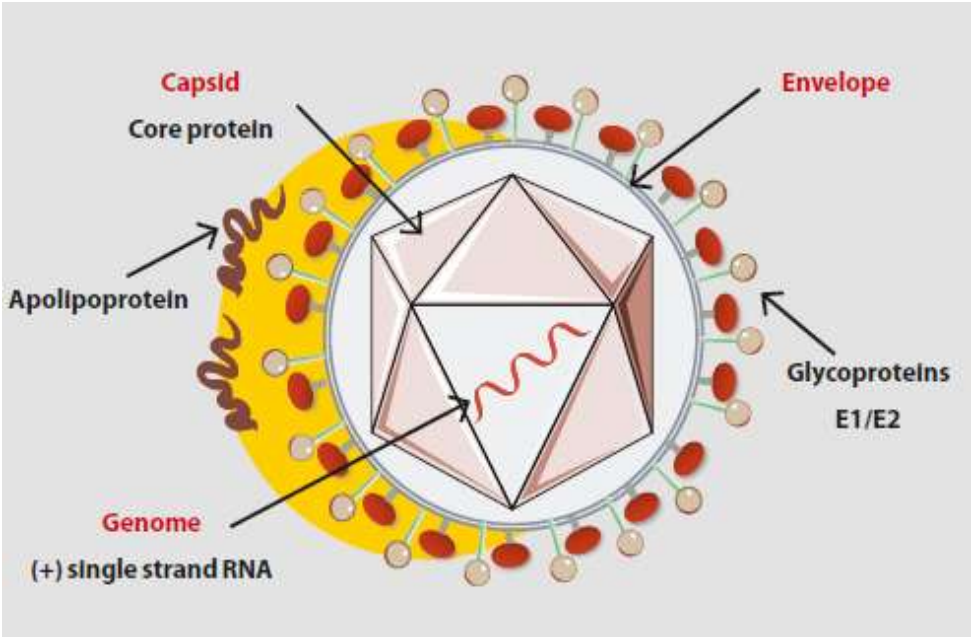

Figure 1: The structure of the hepatitis C virus lipoviro-particle **(Falcon et al., 2017).**

- **HCV genotypes & geographical distribution (figure 2)**

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)**.