



EFFECT OF HEPATITIS C ERADICATION WITH DAA ON TYPE II DIABETES MELLITUS CONTROL AS REGARD INSULIN RESISTANCE & LIPID PROFILE

Thesis

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**تأثير القضاء على الإلتهاب الكبدي الوبائي سى بواسطة مضادات
الفيروسات المباشرة على مرض السكري النوع الثاني من حيث
عدم الإستجابة للانسولين ومستوى الدهون بالدم**

رسالة

**توطئة للحصول علي درجة الماجستير في الباطنة العامة
مقدمة من**

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٢٠٢٠

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لسببانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

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LIST OF ABBREVIATIONS

AASLD	American Association for the Study of liver disease
Ab	Antibody
AIDS	Acquired immunodeficiency disease
AFP	Alpha FetoProtein
ALT	Alanine aminotransferase
AST	Aspartat aminotransferase
BMI	Body Mass Index
CBC	Complete Blood Picture
CD 8	Cluster of Differentiation 8
CDC	Centers for Disease Control and Prevention
CHC	Chronic Hepatitis C
CTP	Child Turcotte Pugh
CV	CardioVascular
CYP	Cytochrome
DAAs	Direct Acting Antiviral Agents
DCV	Daclatasvir
DM	Diabetes Mellitus
DNA	Deoxyribonucleic Acid
EASL	European Association for the Study of the Iver
ECM	Extracellular Matrix
FAQ	Frequent Asked Question
FIB-4	Fibrosis 4
GFR	Golmerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
GLUT4	Glucose Transporter-4
GPBA	G Protein Coupled Bile Acid Receptor
HbA1c	Hemoglobin A1c
HBV	Hepatitis B Virus
HBs Ag	Hepatitis B Surface Antigen
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Viru
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance

List of Abbreviations

HSC	Hepatic Stellate Cells
IDUs	Injecting Drug Users
IFN	Interferon
Igs	Immunoglobulin
IL 6	Interleukin 6
INR	International Normalized Ratio
IR	Insulin Resistance
IRS-1	Insulin Receptor Substrate 1
LDL	Low Density Lipoprotein
LP	Lichen Planus
LPV	Lipoviric Particle
MCV	Mixed Cryoglobulinemic Vasculitis
MELD	Model End Stage Liver Disease
NS5A	Non Structural Protein 5A
OGTT	Oral Glucose Tolerance Test
PAN	Polyarteritis Nodosa
PCR	Polymerase Chain Reaction
PCT	Porphyria Cutanea Tarda
PEG-IFN	Pegylated Interferon
PWID	Patients Who Inject Drugs
RBV	Ribavirin
SD	Standard Deviation
SOCS3	Suppressors of cytokine signaling 3 proteins
SLE	Systemic lupus erythematosus
SOF	Sofosbuvir
SPSS	Statistical Package of Social Science Software
SVR	Sustained Virological Response
T2D	Type 2 Diabetes
TC	Total Cholesterol
TGs	Triglycerides
TGR5	transmembrane G-protein coupled bile acid receptor
TNF	Tumor Necrosis Factor
TRPV1	Transient Receptor Potential Vanilloid
US	United States
UTR	UnTranslated Regions
WHO	World Health Organization
WK	Week

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ABSTRACT

Background: Patients with chronic hepatitis C have both higher prevalence of diabetes mellitus type 2 (T2DM) and increased cardiovascular risk compared to never infected people. The patients with chronic HCV infection can have fatty liver, hypobetalipoproteinemia, and hypercholesterolemia that may cause lipid and lipid protein metabolism disorders.

Objective: To determine the effect of HCV eradication (SVR 12) on type II Diabetic patients as regard insulin resistance & lipid profile.

Patients and Methods: This study was conducted at the gastroenterology and hepatology unit, Ain shams university hospital and Ahmed Maher teaching hospital, Written informed consent was obtained from all subjects before participating in this study. 100 Egyptian patients with chronic hepatitis C and type II Diabetes mellitus were recruited and received (sofosbuvir & daclatasvir) for 3 months. patients continue on same antidiabetics all over the study.

Results: The data from the present study provide evidence of an improvement in IR after clearance of HCV by oral DAA regimen. On the basis of these data, it is possible to hypothesize that HCV clearance by DAAs improving IR and reducing stress on beta-cell function prevents or delay the development of type 2 diabetes mellitus and/or metabolic syndrome in chronic HCV infected patients.

Conclusion: The overall data of this study show that glycemic control improves in patients with diabetes after DAA induced SVR. Patients not only have an improvement in HbA1c level after achieving SVR, they are also less likely to require insulin. the viral clearance due to DAA also led to an improvement of glucose metabolism associated with a global worsening of lipid profile. The HCV clearance by DAA treatment reverses or improves IR and reduces stress on beta-cell function by emphasizing the role of HCV in the development of IR and that this result can prevent IR-related pathological conditions such as worsening liver fibrosis, development of type 2 diabetes, metabolic syndrome and cardio-vascular disorders.

Keywords: Proliferator-activated receptor alpha, tumor necrosis factor alfa, Direct-acting antivirals, type 2 diabetes mellitus

INTRODUCTION

HCV infection and diabetes are severe health problems worldwide, especially in the developing countries (***Waheed et al., 2011***). A range of extra-hepatic manifestations such as arthralgia, thyroiditis and diabetes are linked with HCV infection (***Safi, 2014***).

Studies have shown that patients infected with HCV have more glucose intolerance than the general population as well as when compared to patients with other liver diseases, including hepatitis B (***White et al., 2008***).

There seem to be three important clinical consequences of the association between HCV and IR/DM. First, HCV infection by itself may be a risk for development of DM. Second, presence of DM and IR may accelerate progression of liver disease in patients infected with HCV (***Younossi and McCullough, 2009***). Finally, HCV-infected patients with IR and DM seem to have poorer response to anti-HCV regimen. (***Romero-Gomez et al., 2005***).

IR and its associated hyperinsulinemia represent the main underlying mechanism of abnormal glucose homeostasis in patients with DM. It has been postulated that insulin in the setting of hyperinsulinemia promotes and accelerates fibrosis progression in patients with HCV through several mechanisms, including hepatic steatosis,

tumor necrosis factor alfa (TNFA) production, and impaired expression of peroxisome proliferator-activated receptor alpha (PPAR α) (*Dharancy et al., 2005*)

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AIM OF THE WORK

To determine the effect of HCV eradication (SVR 12) on type II Diabetic patients as regard insulin resistance & lipid profile.

HEPATITIS C PATHOPHYSIOLOGY

Hepatitis C is an infection caused by the hepatitis C virus (HCV) that attacks the liver and leads to inflammation. It is a cause of both acute and chronic hepatitis. The World Health Organization (WHO) estimates about 71 million people globally have chronic hepatitis C, with about 399,000 dying from this infection as primarily due to cirrhosis and hepatocellular carcinoma (HCC). (*"Hepatitis C Questions and Answers for Health Professionals | CDC", 2018*)

Pathophysiology

Hepatitis C virus (HCV) is a spherical, enveloped, single-stranded RNA virus belonging to the family Flaviviridae, genus Flavivirus.

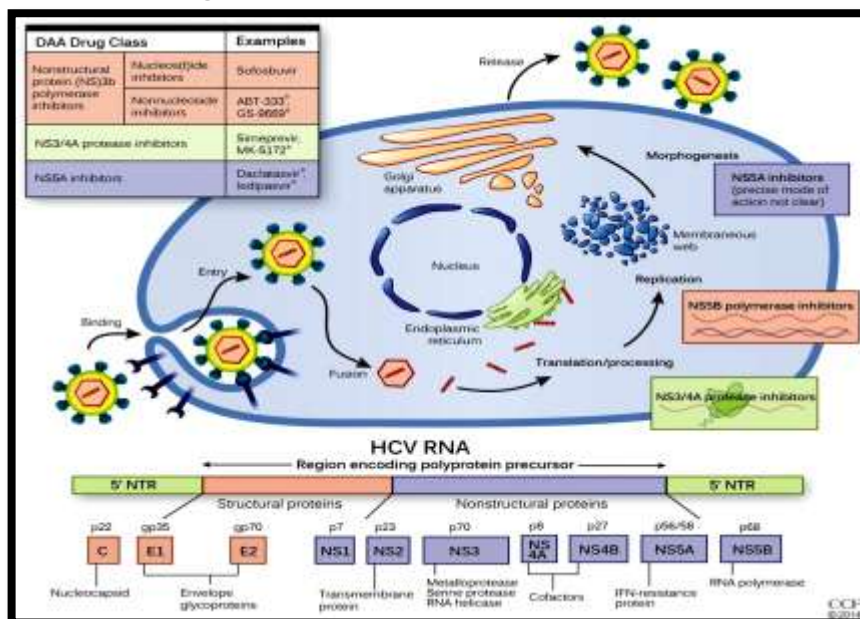


Figure (1): HCV genome (Calabrese and Cacoub, 2015)

The HCV genome consists of a single, open reading frame and two untranslated, highly conserved regions, 5'-UTR and 3'-UTR, at both ends of the genome. The genome has approximately 9500 base pairs and encodes a single polyprotein of 3011 amino acids that are processed into 10 structural and regulatory proteins.

The natural targets of HCV are hepatocytes and, possibly, B lymphocytes. Viral clearance is associated with the development and persistence of strong virus-specific responses by cytotoxic T lymphocytes and helper T cells.

In most infected people, viremia persists and is accompanied by variable degrees of hepatic inflammation and fibrosis. Findings from studies suggest that at least 50% of hepatocytes may be infected with HCV in patients with chronic hepatitis C.

Nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, NS5B, and p7), whose proteins function as helicase-, protease-, and RNA-dependent RNA polymerase, although the exact function of p7 is unknown. These nonstructural proteins are necessary for viral propagation and have been the targets for newer antiviral therapies, such as the direct-acting antiviral agents (DAAs). NS2/3 and NS3/4A are proteases responsible for cleaving the HCV polyprotein. NS5A is critical for the assembly of the cytoplasmic membrane-bound replication complex; one region within NS5A is linked to an interferon (IFN)