INSULIN RESISTANCE IN CHRONIC HEPATITIS C VIRUS PATIENTS RECEIVING DIRECT ACTING ANTIVIRAL DRUGS

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by

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مقاومة الانسولين في المرضي المصابين بالتهاب الكبدي الوبائي المزمن (سي) الذين يتناولون مضادات الفيروسات المباشرة

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List of Abbreviation

AHC: acute hepatitis C.

ApoE :apolipoprotein E.

CCL2: chemokine (C-C) motif ligand 2

CHC : chronic hepatitis C.

cLD : cytosolic lipid droplets.

DAAs : direct-acting antivirals.

EDHS :Egyptian Demographic Health Survey

EIAs : enzyme immuno assays.

EMRO : Eastern Mediterranean Regional office

ER: endoplasmic reticulum.

FDA :food and drug administration.

GAGs :glycosaminoglycans.

GWAS: genome-wide association studies.

HOMA: homeostasis model assessment.

HVR1 : the hypervariable region 1 .

IVDUs : intravenous drug users.

IR : insulin resistance.

IRES:internal ribosome entry site.

IRS : insulin receptor substrate.

kDa: kiloDalton.

LDL : low density lipoproteins.

MC: Mixed cryoglobulinemia.

MELD : model for end stage liver disease.

mTOR :mechanistic target of robamycin .

NASH : non-alcoholic steatohepatitis.

NATs : nucleic acid amplification system.

NCCVH: National Committee for the Control of Viral Hepatitis.

NPC1L1: Niemann-Pick C1-like 1.

NTPase: nucleoside triphosphatase

NTRs: non-translated regions.

OSA : osteoarthritis.

PCOS :polycysticovarian syndrome.

PI3K:phosphoionozotide 3 kinase.

RAS :reticular activating system.

rNTP :ribonucleoside triphosphates.

SRB1 : Scavenger receptor class B member 1

SVR : a sustained virological response.

T2DM : type 2 diabetes mellitus.

TMA: transcription mediated amplification .

US : United Status.

VAP :virion associated protein.

VLDL : very low density lipoproteins.

WAT: white adipose tissue.

WHO: world health organization.

YB-1: Y-box-binding protein 1.

Introduction

Hepatitis C virus (HCV) is a globally prevalent pathogen and a leading cause of death and morbidity ***(Cooke et al., 2013).***

The recent estimates of disease burden show an increase in seroprevalence over the last 15 years to 2.8%, equating to >185 million infections worldwide. Persistent HCV infection is associated with the development of liver cirrhosis, hepatocellular carcinoma, liver failure, and death ***(Hanafiah et al., 2013).***

According to the studies published between 1989 and 2013, HCV exhibits high genetic diversity, characterized by regional variations in genotype prevalence ***(Messina et al., 2015).***

Historically, HCV drug therapy has depended on interferon-α (administered by injection) and ribavirin over many months and is associated with severe side effects ***(Ford et al., 2012).***

A greater understanding of the HCV genome and proteins has enabled efforts to improve efficacy and tolerability of HCV treatment. Notably, this has led to the development of multiple direct-acting antivirals (DAAs), which are medications targeted at specific steps within the HCV life cycle. DAAs are molecules that target specific nonstructural proteins of the virus and results in disruption of viral replication and infection ***(Poordad and Dieterich, 2012).***

The first generation of new DAAs were given in combination with interferon and ribavirin give more better result, but it added some burden on the side effect ***(Poordad et al., 2013).***

The use of second-generation DAA therapies with minimal side effects and shortened courses of therapy are associated with cure rates of more than 90% in Phase II or III studies ***(Lawitz et al., 2013).***

Multiple DAA therapies targeting distinct HCV proteins have been developed. If DAAs are made affordable, the treatment of HCV across the globe will become a realistic option for the first time ***(Lawitz et al., 2014).***

Genotype 4 HCV is the most common HCV genotype in Middle East and has spread to other areas due to immigration ***(Lawitz et al., 2015).***

Sofosbuvir is approved by the Food and Drug Administration on December 6, 2013, for the treatment of chronic HCV infection, Sofosbuvir is a 400-mg tablet to be taken once daily with or without food for 12 weeks as a component of a combination antiviral treatment regimen ***(Cha and Budovich, 2014).***

Recently, Daclatasvir is indicated for use with Sofosbuvir for the treatment of patient with chronic HCV infection for 12 week. The recommended dosage of Daclatasvir is 60 mg, taken orally, once daily in combination with sofobuvir ***(David et al., 2015).***

And also recently new drug developed called Ledipasvir/sofosbuvir (Harvoni) is a two-drug combination for the treatment of hepatitis C. It is administered as a single daily pill containing 90 mg of the ledipasvir and 400 mg of sofosbuvir ***(Keating, 2015).***

Qurevo (Paritaprevir/Ritonavir/Ombitasvir) is one of direct anti viral drugs that has successfully demonstrate a favorable safety and efficacy profiles, without necessitating co-administration with interferon ***(Curtler, 2015).***

Epidemiological studies have suggested a linkage between type 2 diabetes and chronic HCV infection. However, the presence of additional factors such as obesity, aging, or cirrhosis prevents the establishment of a definite relationship between these 2 conditions ***(Abdelaziz et al., 2016).***

Hepatitis C virus infection is linked to greater insulin resistance. Although HCV itself is a candidate for the development of insulin resistance (IR). ***(Kappel et al., 2012).***

Although a definite cause-and-effect relationship between HCV and diabetes has not been established, the successful eradication of HCV may result in an improvement of IR. However, the impact of viral eradication on downstream consequences of IR, such as impairment of glucose metabolism, has not been clearly established ***(Delgado et al., 2013).***

The use of homeostasis model assessment (HOMA)-IR to assess insulin sensitivity suggested that interferon use were clearly associated with insulin resistance ***(Brandman et al., 2012).***

Aim of the work

The aim of this work is to assess:

- The relation between chronic HCV infection and insulin resistance in Egyptian patients.
- The effect of new direct acting antiviral drugs (DAAs) on insulin resistance.
- The effect of insulin resistance on the response to DAAs.

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