

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

Thesis

Submitted for partial fulfillment of MD degree

In

Internal Medicine

by

Emad Nabil George Marcos

Master Degree in Internal Medicine

Faculty of Medicine - Ain Shams University

Under supervision of

Prof. Dr. Hesham Ezz Eldin Said

Professor of Internal Medicine, Gastroenterology and Hepatology

Faculty of Medicine -Ain Shams University

Dr. Zainab Ahmed Ali-Eldin

Assistant Prof. of Internal Medicine, Gastroenterology and Hepatology

Faculty of Medicine -Ain Shams University

Dr. Eslam Safwat Mohamed

Assistant Prof. of Internal Medicine, Gastroenterology and Hepatology

Faculty of Medicine -Ain Shams University

Dr. Yasser Omar Abdel Rahman

Lecturer of Internal Medicine Gastroenterology and Hepatology

Faculty of Medicine - Ain Shams University

**Faculty of Medicine
Ain Shams University**

2017

مقاومة الانسولين في المرضى المصابين بالتهاب الكبد الوبائي المزمن (سي) الذين يتناولون مضادات الفيروسات المباشرة

رسالة

توطئة للحصول علي درجة الدكتوراه في أمراض الباطنة العامة
مقدمة من

الطبيب/ عماد نبيل جورج مرقص

ماجستير أمراض الباطنة العامة

كلية الطب- جامعة عين شمس

تحت إشراف

أ.د. هشام عز الدين سعيد

أستاذ أمراض الباطنة والجهاز الهضمي والكبد

كلية الطب - جامعة عين شمس

د. زينب أحمد علي الدين

أستاذ مساعد أمراض الباطنة و الجهاز الهضمي والكبد

كلية الطب - جامعة عين شمس

د. إسلام صفوت محمد

أستاذ مساعد أمراض الباطنة و الجهاز الهضمي والكبد

كلية الطب - جامعة عين شمس

د. ياسر عمر عبد الرحمن

مدرس أمراض الباطنة و الجهاز الهضمي والكبد

كلية الطب - جامعة عين شمس

كلية الطب

جامعة عين شمس

٢٠١٧

Acknowledgment

Praise to "Allah", the Most Gracious and the Most Merciful Who Guides Us to the Right Way.

I would like also to express my deep gratitude to **Prof. Dr. HeshamEzzEldin Said**, Professor of Internal Medicine, Gastroenterology and Hepatology, Faculty of Medicine -Ain Shams University. who had made a great effort with me in this thesis. for his precious guidance, wise instructions, meticulous supervision, valuable experience and time, endless cooperation and true concern to accomplish this work in the best possible image. For the time he gave to me, his support and sincere help.

It is a great honor to express my deep gratitude and cordial appreciation to **Dr. Zainab Ahmed Ali-Eldin**, Assistant Prof. of Internal Medicine, Gastroenterology and Hepatology, Faculty of Medicine -Ain Shams University. who gave me much of her effort, experience and close supervision throughout the work. She provided me continuous encouragement and support. Her generous assistance and meticulous guidance had a pivotal role in the completion of this study. For providing me the experience, cooperation and close supervision throughout the work.

I would like to express my deep gratitude to **Dr. EslamSafwat Mohamed**, Assistant Prof. of Internal Medicine, Gastroenterology and Hepatology, Faculty of Medicine -Ain Shams University. for his great encouragement, constant support. Without his continuous help this work would never have been accomplished. His patience and willingness to provide continuous guidance have been instrumental in bringing the study to completion.

My appreciation and deepest thanks to **Dr. Yasser Omar Abdel Rahman**, Lecturer of Internal Medicine Gastroenterology and Hepatology, Faculty of Medicine - Ain Shams University. for his great assistance .

I would like also to express my deep gratitude to **Prof. Dr. Mohamed Said Abdel Aziz**, Professor of endemic medicine Cairo university. who had made a great effort with me in this thesis. for his endless cooperation and true concern to accomplish this work.

I would like to express my deep gratitude to **Dr. Hossam Mohamed FakryDeabes**, Head of Medical center of Damnhour liver institute , for his great encouragement, constant support.

*My great appreciation is extended to all those who shared either practically .
or morally in the accomplishment of this work.*

CONTENTS

Chapter	Page
Acknowledgment	<i>i</i>
List of Contents	<i>ii</i>
List of Figures	<i>ii</i>
List of Tables	<i>iv</i>
1. <i>Review of Literature</i>	<i>1</i>
2. <i>Patients and methods</i>	<i>80</i>
3. <i>Results</i>	<i>91</i>
4. <i>Discussion</i>	<i>112</i>
5. <i>Summary</i>	<i>127</i>
6. <i>Conclusion</i>	<i>131</i>
7. <i>Recommendation</i>	<i>132</i>
8. <i>References</i>	<i>133</i>
<i>Protocol</i>	
<i>Arabic summary</i>	

List of Figures

	Page
Fig (1): “hepatitis c virus	5
Fig (2): HCV genome and proteins.	9
Fig (3): Electron micrograph of hepatitis C virus purified from cell culture. Scale: black bar = 50 nanometres	13
Fig (4):HCV entry.	14
Fig (5) :A simplified diagram of the HCV replication cycle	15
Fig (6):HCV replication and assembly.	16
Fig (1): description of baseline insulin resistance before treatment	95
Fig (2): description of insulin resistance after end of treatment.	96
Fig (3):Description of change in insulin resistance at end of treatment among study cases	97
Fig (4): PCR 12 wks after end of treatment	100
Fig (5):percent of cases on dual or triple therapy	100
Fig (6):male and female PCR count before treatment	103
Fig (7):Comparison between insulin resistance before and after treatment	105
Fig (8):Comparison between negative and positive PCR cases 12 weeks after end of treatment as regard to IR before treatment	106

List of Tables

	Page
Table 1: IFN-free combination treatment regimen available as valuable option for each HCV genotype	37
Table (1): Description of personal and medical data among all studied cases	91
Table (2): Description of Ultrasound findings among cases	92
Table (3): Description of BMI among study cases	92
Table (4): Description of baseline lab findings among study cases and after end of treatment.	93
Table (5): Description of baseline (FBS, Fasting insulin, HOMA IR and insulin resistance) before treatment and at the end of treatment among study cases	94
Table (6): Description of insulin resistance after treatment among cases with baseline resistance	96
Table (7): Description of change in insulin resistance at end of treatment among study cases	97
Table (8): Description of treatment received (dual or triple) and PCR at end of treatment and 12 weeks after treatment (SVR) among study cases	98
Table (9): Relation between personal data and Insulin resistance before treatment	99
Table (10): Correlation between baseline PCR and other parameters	101
Table (11): Relation between each of personal, medical, ultrasound data and baseline PCR count.	102
Table (12): Comparison between insulin resistance before and after treatment	103
Table (13): Comparison between negative and positive PCR cases 12 weeks after end of treatment (sustained viral response) as regard insulin resistance before and at end of treatment	104
Table (14): Comparison between dual and triple treatment as regard	106

insulin resistance at end of treatment and the change in insulin resistance at end of treatment	
Table (15): Comparison between dual and triple treatment as regard insulin resistance before treatment and at end of treatment	107
Table (16): The difference in (SVR12) between patient using either dual or triple therapy	108
Table (17): Comparison between baseline and at end of treatment ALT, AST and albumin	109
Table (18): Comparison between baseline and at end of treatment FBS, fasting insulin and HOMA IR	109
Table (19): Relation between BMI and each of Insulin resistance before treatment, after treatment and Change in IR after treatment	110
Table (20): Comparison between Negative and positive PCR as regard Change in HOMA IR after treatment	111

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.

Abbreviation

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 sofosbuvir (*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.

Reference

Abdelaziz, S.B.; Galal, S.Y.; Sedrak, S.A.; Shaheen, S.D. (2016): Association of Hepatitis C Virus Infection and Type 2 Diabetes in Egypt: A Hospital-Based Study. *Journal of Diabetes Mellitus*, 6, 77-89.

Brandman, D.; Bacchetti, P.; Claudia, E. A.; Jacquelyn, J. M. Khalili, M. (2012): Impact of Insulin Resistance on HCV Treatment Response and Impact of HCV Treatment on Insulin Sensitivity Using Direct Measurements of Insulin Action. *Diabetes Care*; 35(5): 1090–1094.

Cha, A. and Budovich, A. (2014): Sofosbuvir: A New Oral Once-Daily Agent for The Treatment of Hepatitis C Virus Infection P T.; 39(5): 345–352.

Cooke, G.S.; Lemoine, M; Thursz, M; Gore, C; Swan, T; Kamarulzaman, A. (2013): Viral hepatitis and the Global Burden of Disease: a need to regroup. *J Viral Hepat.*; 20: 600-601.

David, C. W. (2015): Hepatitis C Organism-Specific Therapy 2015 emedicine, American Association for the Study of Liver Diseases [medscape.com/article/2072024-overview](https://www.medscape.com/article/2072024-overview).

Delgado-Borrego, A.; Kamegaya, Y.; Jordan, S.H.; Agrawal, S.; Valim, C.; Chung, R.T. (2013): HCV synergizes with body weight in the promotion of insulin resistance. *J Viral Hepat*; 18: 135–141.

Ford, N.; Kirby, C.; Singh, K.; Mills, E.J.; Cooke, G.; Kamarulzaman, A. (2012): Chronic hepatitis C treatment outcomes