Diabetes mellitus and peripheral insulin resistance (IR) in patients with chronic hepatitis C treated by interferon plus ribavirin therapy versus untreated

Thesis for partial fulfillment of MD degree in internal medicine

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INTRODUCTION

Patients with hepatitis C virus (HCV) infection present higher risk of developing type-2 diabetes mellitus (DM). However, the mechanism of this association and the role of antiviral treatment are still unclear.
(Mello V, ET AL., 2006)

Insulin resistance (IR) is known to be associated with the visceral adipose tissue area. Elucidation of the relationship between hepatitis C virus (HCV) and IR is of great clinical relevance, because IR promotes liver fibrosis.
(Yoneda M, ET AL., 2007)

Several methods for evaluating Insulin resistances in humans have been reported: fasting plasma insulin (FIRI) levels, homeostasis model assessment (HOMA), insulin tolerance test, insulin suppression test, steady-state plasma glucose method, and minimal model technique. Among these indeces, FIRI and the insulin resistance index (IR) by HOMA, calculated from FIRI and fasting plasma glucose (FPG) levels, are likely to be the most simple and repeatable indeces in diabetic outpatient clinics.
(Noran JJ, ET AL., 2005)

Patients with nonalcoholic fatty liver disease (NAFLD) and normal alanine aminotransferase (ALT) have a milder disease and should undergo liver biopsy.
(Fracanzani AL, ET AL., 2008)

Alterations in glucose metabolism and insulin resistance in subjects with normal ALT should also be considered in the selection of NAFLD cases for histological assessment of disease severity and progression.
(Wouters K, ET AL., 2008)

AIM OF WORK

To evaluate peripheral insulin resistance IR and prevalence of diabetes mellitus in patients of chronic hepatitis C before treatment and after 24-week course therapy with peg interferon plus ribavirin.

Patient & Methods

The study will be conducted on 60 patients of chronic hepatitis C & 15 patients without hepatitis C infection as a control Group all of them are not diabetic.
-patients are from Kobri El kobba military hospital and ain shams university hospital.

-- The 60 Patients with chronic hepatitis C will be divided into two groups group (B1) & group (B2).
-- Group (B2) will include 30 patients of chronic hepatitis C treated by interferon plus ribavirin therapy & group (B1) will include 30 patients of chronic hepatitis C but still untreated.

-- All patients & controls will be subjected for:

1-Full history taking.
2-Full clinical examination.
3-Laboratory tests include: Fasting and postprandial blood sugar ALT, AST, HBsAg, HCVAb, S.Creatinine, Na, K, CBC, ESR, complete lipid profile, PT, PTT, S. Albumin & HBA1C.
4- Abdominal Ultrasound.
5- Homeostasis model assessment (HOMA-IR**)**

$$\text{HOMA-IR} = \frac{\text{fasting plasma insulin (μIU/mL)} \times \text{fasting plasma glucose (mmol/L)}}{22.5}$$

6- PCR for all patients with chronic hepatitis C

Exclusion Criteria

1- HBV infection.
2- Patients with cirrhotic liver.
3- Chronic renal diseases.
4-Diabetis mellitus

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List of abbreviations

(AACE) …….American Association of Clinical Endocrinologists
(ALT)……...alanine aminotransferase
(BUN)…….... Blood urea nitrogen
(BMI) ……..Body mass index
(CBC)……...complete blood count
(CHD)…… Coronary heart disease
(CI)……..confidence interval
(CRP)……...C-reactive protein
(CVD)……..cardiovascular disease
(DM)……diabetes mellitus
(EIA)……....enzyme immunoassay
(FDA)……...Food and Drug Administration
(FIRI)…….. Fasting insulin resistance index
(FPG)……... f asting plasma glucose
(GLP-1)…….…glucagon like peptide 1
(GLUT-4)…….….Glucose transporter 4
(HBV)……...hepatitis B virus
(HBsAg)……hepatitis B surface antigen
(HCC)……...hepatocellular carcinoma
(HCV)…….. Hepatitis C virus
(HDL-C)……...High-density lipoprotein cholesterol
(HIV)……Human immunodeficiency virus
(HLA)……humal leucocyte antigen
(HPV)……human papiloma virus
(HOMA)…….....Homeostasis model assessment
(IDF)……International Diabetes Federation
(IFG)……impaired fasting glucose
(IFN)……..interferon
(Ig)……immunoglobulin
(IGT)…….... Impaired glucose tolerance
(IGF-1)……..insulin like growth factor–1
(IL)…….....Interleukins

(IR)……insulin resistance
(IRS-1)……..insulin receptor substrate-1
(ISI)……...insulin sensitivity index
(LDL)……low-density lipoprotein
(LT)……...liver transplantation
(MS)……..multiple sclerosis
(NASH)…… non-alcoholic steatohepatitis
(NCEP/ATP III)……..National Cholesterol Education Program/Adult Treatment Panel III
(PAI-1)…….plasminogen activator inhibitor–1
(PCOS)…… Polycystic ovary syndrome
(PCR)……polymerase chain reaction
(PEG-IFN) ……...pegylated interferon
(PG-AUC)……... area under the curve of plasma glucose
(PPARs) ……peroxisome proliferator-activated receptors
(OGTT)……oral glucose tolerance test
(SI-AUC)……...area under the curve of serum insulin
(SVR)……sustained virological response
(TMA)……transcription-mediated amplification
(TNF)……tumour necrosis factor
(TPO)……thyroid perioxidase
(TZDs)……Thiazolidinediones
(WHO)……..World Health Organization

Hepatitis C

Background

The World Health Organization (WHO) estimates 170 million individuals worldwide are infected with hepatitis C virus (HCV). However, the prevalence of HCV infection varies throughout the world. For example, in 2000, Frank et al reported that Egypt has the highest number of reported infections, largely attributed to the use of contaminated parenteral antischistosomal therapy. **(Frank C et al., 2000).** This has led to a mean prevalence of HCV antibodies in persons in Egypt of 22%. According to the US Centers for Disease Control and Prevention, an estimated 1.8% of the US population is positive for HCV antibodies. Because 3 of 4 seropositive persons are also viremic, this corresponds to an estimated 2.7 million people with active HCV infection nationwide. Infection due to HCV accounts for 20% of all cases of acute hepatitis, an estimated 30,000 new acute infections, and 8000-10,000 deaths each year in the United States **(Lauer GM et al., 2009).**

Medical care costs associated with the treatment of HCV infection in the United States are estimated to be more than $600 million a year. Most patients infected with HCV have chronic liver disease, which can progress to cirrhosis and hepatocellular carcinoma (HCC). Chronic infection with HCV is one of the most important causes of chronic liver disease and, according to a report by Davis et al from 2003, the most common indication for orthotopic liver transplantation (LT) in the United States **(Davis GL et al., 1999).**

HCV is a spherical, enveloped, single-stranded RNA virus belonging to the Flaviviridae family and Flavivirus genus. In 2001, Lauer and Walker reported that HCV is closely

related to hepatitis G, dengue, and yellow fever viruses. HCV can produce at least 10 trillion new viral particles each day. RNA-dependent RNA polymerase, an enzyme critical in HCV replication, lacks proofreading capabilities and generates a large number of mutant viruses known as quasispecies. These represent minor molecular variations with only 1-2% nucleotide heterogeneity. HCV quasispecies pose a major challenge to immune-mediated control of HCV and may explain the variable clinical course and the difficulties in vaccine development **(Batts KP et al., 2009).**

The HCV genome consists of a single, open reading frame and 2 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 **(Batts KP et al., 2009).**

Structural components include the core and 2 envelope proteins, E1 and E2. Two regions of the E2 protein, designated hypervariable regions 1 and 2, have an extremely high rate of mutation, thought to result from selective pressure by virus-specific antibodies. The envelope protein E2 also contains the binding site for CD-81, a tetraspanin receptor expressed on hepatocytes and B lymphocytes that acts as a receptor or coreceptor for HCV.

The nonstructural components include 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. One region within NS5A is linked to an interferon (IFN) response and is called the IFN sensitivity-determining region. These enzymes are critical in viral replication and are attractive targets for future antiviral therapy **(Beaulieu PL et al., 2006).**