Value of serum adiponectin level in the assessment of hepatic necroinflammation in obese and non obese chronic hepatitis (C) patients

Thesis
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Introduction:

Hepatitis C Virus (HCV) is recognized as a major threat to global public health. An estimated 170 million people worldwide are infected, most of them chronically infected and at risk for liver cirrhosis and hepatocellular carcinoma (HCC) **(Pybus et al., 2003).**

Egypt has possibly the highest HCV prevalence in the world; 10%-20% of the general population are infected and HCV is the leading cause of HCC and chronic liver disease in the country **(Pybus et al., 2003).**

Hepatitis C virus (HCV) infection, although a viral infection of the liver, often presents features of the metabolic syndrome (insulin resistance, diabetes mellitus and liver steatosis) **(Hui et al., 2003).**

Adiponectin is an adipocytokine secreted by adipocytes, with antidiabetic, antilipogenic and antiatherogenic actions **(Weyer et al., 2001).** Low plasma levels of adiponectin contribute to the pathogenesis of insulin resistance, type II diabetes mellitus and cardiovascular diseases in obese or overweight patients **(Guerre-Millo, 2008).**

Adiponectin directly affects the inflammatory response by regulating both the production and activity of cytokines **(Ouchi et al., 2000)** and can also act as an antiapoptotic agent in a variety of cell types **(Kobayashi et al., 2004).**

However, the value of adiponectin in the prediction of underlying hepatic necroinflammation and insulin resistance in patients with chronic hepatitis C remains to be elucidated.

Aim of the work:

To assess the value of serum adiponectin level in the prediction of hepatic necroinflammation in patients with chronic hepatitis C and to correlate serum adiponectin level with parameters exploring insulin resistance in these patients.

Patients and methods:

This study will be performed on 80 patients with chronic hepatitis C attending **the liver disease outpatient clinic at Ain Shams University Hospital.**

Subjects will be divided into 2 groups:

A- 40 patients with chronic hepatitis C and overweight (BMI >25).

B- 40 patients with chronic hepatitis C only (BMI up to 25).

The study will be performed also on 40 persons as 2 control groups

C- 20 persons with normal hepatic profile, HCV Ab –ve and overweight (BMI >25).

D- 20 persons with normal hepatic profile, HCV Ab –ve only (BMI up to 25).

The patient and control groups will be in the same age range as much as possible. No specific treatment will be given to any group.

All persons will be subjected to the following:

1- Full history taking.

2- Full clinical examination including BMI and abdominal examination.

3- Laboratory investigations:

- Fasting and post prandial blood glucose.
- Liver function test: ALT, AST, Bilirubin (total and direct), alkaline phosphatase, GGT, albumin, prothrombin time.
- Renal function tests: s. creatinine, BUN, Na, K.
- CBC.
- Lipid profile: fasting triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol.
- HCV-Ab (3^{rd} generation ELISA).
- PCR-HCV RNA Quantitative.
- HBs Ag, HBc Ab.
- ANA.
- Serum insulin, serum C-peptide.

- Insulin resistance will be calculated using the homeostasis model assessment (HOMA) method as per the following equation: insulin resistance (HOMA- IR) = fasting insulin (μU/mL) x fasting glucose (mmol/L)/22.5 **(Mohammad Alizadeh et al., 2006).**

- Serum adiponectin level.

4- Abdominal ultrasonography.

5- Liver biopsy: For group A and B only.

- Document HCV hepatitis.

- Degree of necroinflammation (activity).

- Degree of fibrosis (staging).

- Degree of steatosis.

According to the modified histologic activity index (HAI) of Ishak **(Ishak et al., 1995).**

Liver biopsy will be done after checking the coagulation profile and exclusion of any medication that could increase the risk of bleeding. Liver biopsy will not be done in case of uncooperative patient, prolonged prothrombin time (by more than 3 seconds), low platelets (< 80 000/mL), ascites or extrahepatic cholestasis.

Exclusion criteria:

The following patients will be excluded from the study:

1- Patients with liver cirrhosis.

2- Patients with diabetes mellitus.

3- Patients with other liver diseases (HBV, autoimmune, alcoholic).

4- Patients with renal impairment or failure.

5- Patients refusing to be entitled in the study.

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Chapter (1)

Hepatitis C virus

Introduction:

Hepatitis C Virus (HCV) is a member of the flaviviridae family and is a major pathogen of hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC) ***(Shepard et al., 2005)***.

It is estimated that 3.3% of the population globally (lower in Europe 1.03% and highest in Africa 5.3%) are chronically infected with this viral pathogen ***(Hepatitis C, 2009; Raza et al., 2007)***.

Egypt has the highest HCV prevalence in the world; 10%-20% of the general population are infected ***(El-Zayadi et al., 2001; Habib et al., 2001)***.

In industrial countries, HCV accounts for 20% of acute and 70% of chronic cases of hepatitis ***(Farhana et al., 2009)***

Major HCV infections lead to chronic hepatitis, which results in progressive fibrosis ultimately resulting in cirrhosis, liver failure and an increased risk of hepatocellular carcinoma ***(Shepard et al., 2005; Jacobs et al., 2005).***

Molecular Virology:

Hepatitis C virus has been classified as a member of the flaviviridae family. All members of this family are small sized enveloped viruses containing single stranded RNA encoding an approximately 9000 amino acid polypeptides (Figure 1) ***(Rosenberg, 2001).***

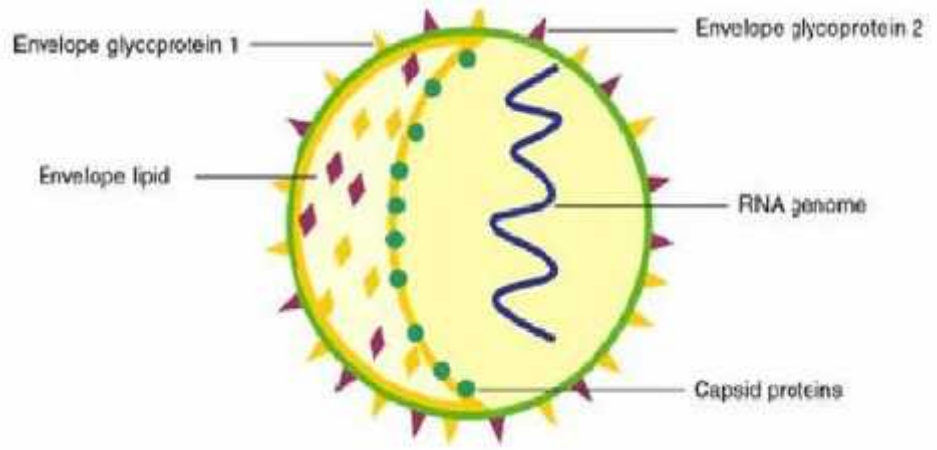

Figure (1): Model structure of HCV ***(Akbar et al., 2009)***.

The viral genome is composed of a 5' non coding region, a long open reading frame encoding a polyprotein precursor of about 3000 amino acids, and a 3' non coding region ***(Sherlock and Dooley, 2002)***. This HCV polyprotein is cleaved into a number of structural and non-structural (NS) proteins ***(Alberti and Benvegnu, 2003)***.

The structural proteins include the core protein and two envelope glycoproteins, E1 and E2 ***(Sherlock and Dooley, 2002)***. Core and non structural proteins (NS2, NS3, NS4A, NS4B, NS5a and NS5B) exert numerous actions in target cells and could play a role in the pathogenesis of chronic liver disease ***(Giannini and Brechot, 2003)***. Their role depends on the target cell type and includes control of cell growth, apoptosis, oxidative stress, and immunomodulation ***(Lai, 2002)***.

The intracellular mechanisms involved in core-induced biologic actions include generation of free radicals, stimulation of mitogen activated protein kinases, and nuclear factor κB activation (Figure 2) ***(Yoshida et al., 2001).***

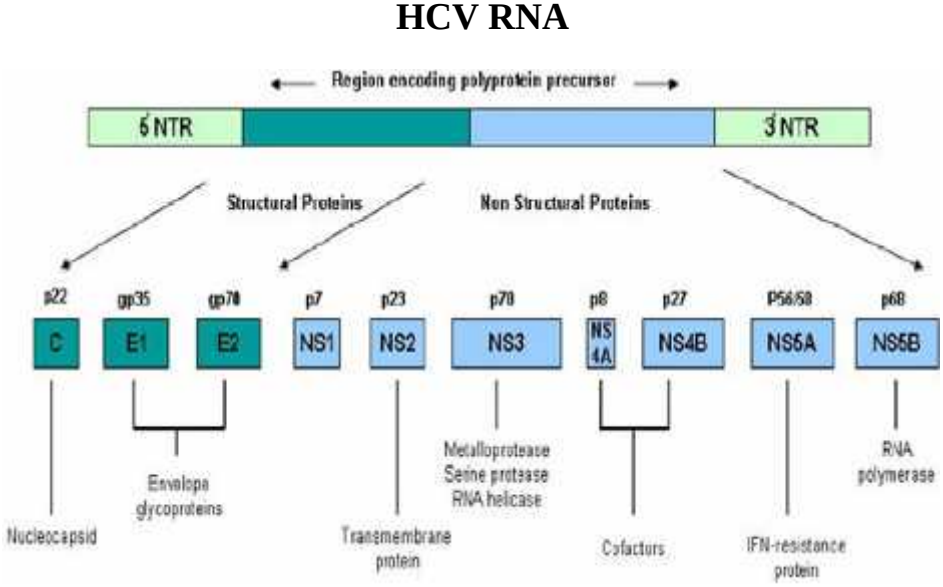

Figure (2): HCV genome organization ***(Akbar et al., 2009)***.