Detection of Serum Adiponectin in patients of Chronic Hepatitis C and its relation to the treatment therapy

Thesis Submitted
For partial fulfillment of Master degree in internal medicine

By

Sally Hussein Ibrahim
M.B.B.CH
Faculty of Medicine
Ain-Shams University

Under supervision of

Prof. Khaled Hassan M.Hemida
Prof.of Internal medicine
Faculty of Medicine
Ain-Shams University

Prof. Ahmed Ali Monies
Prof. of Internal medicine
Faculty of Medicine
Ain-Shams University

Dr. Nevine Ibrahim Musa
Lecturer of Internal medicine
Faculty of Medicine
Ain-Shams University

2013

LIST OF ABBREVIATIONS

AASLD	The American Association for the Study of Liver Disease.
ACRP٣٠	Adipocyte complement-related protein of ٣٠ kDa.
ADIPOR١	Adiponectin receptor ١.
ADIPOR٢	Adiponectin receptor ٢.
AMPK	٥-AMP-activated kinase.
apM١	Adipose most abundant gene transcript ١.
APRI	The AST-to-platelet ratio index.
CAD	Coronary artery disease.
CAPMAS	Central Agency for Public Mobilization and Statistics.
cEVR	Complete early virologic response.
CHC	Chronic hepatitis C infection.
CLDN١	Claudin-١.
CVD	Cardiovascular diseases.
EIA	Enzyme immunoassay.
EDHS	The Egyptian Demographic Health Survey.
ER	Endoplasmic reticulum.
ETR	End-of-treatment response.
EVR	Early virologic response.
fAd	Full-length form of adiponectin.
gAd	Globular fragment of adiponectin.
GBP٢٨	Gelatin-binding protein of ٢٨ kDa.
HAART	Highly active antiretroviral therapy.
HBV	Hepatitis B virus.
HCC	Hepatocellular carcinoma.
HCV	Hepatitis C virus.
HIV	Human Immunodeficiency Virus.
HDL	High-density lipoproteins.
HMW	High molecular weight adiponectin.
HOMA	Homeostasis model assessment.

IKKβ	inflammatory mediator IκB kinase β.
IL-١	Interleukin ١.
IR	Insulin resistance.
IRS	Insulin receptor substrates.
MHC class	Major Histocompatibility class.
MOHP	The ministry of health and population.
NAT	Nucleic acid tests.
NK	Natural Killer cells.
PAMPs	Pathogen-associated molecular patterns.
PCR	Polymerase chain reaction.
pEVR	Partial early virologic response.
PPAR- α	peroxisome proliferator-activated receptor-α.
PPRE	PPAR response elements.
PP٢A	Protein phosphatase ٢A.
RdRp	RNA-dependent RNA polymerase.
RVR	A rapid virologic response.
SR-B١	Human receptor class B type ١.
SVR	Sustained virological response.
T-Cad	T-cadherin.
T٢D	Type ٢ diabetes.
TGFβ	transforming growth factor β.
Th١	T helper cells.
TNF-alpha	Tumor necrosis factor –alpha.
TZD	Thiazolidinediones.
U.S.A	United States of America.

Content

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Adiponectin is an adipocytokine and suggested to have hepato-protective effect. Recent advances in cell biology have shown that adipocytes produce and secrete several bioactive molecules which are collectively referred to as adipocytokines. An adipocyte-specific secretory protein, adiponectin ***(Tary et al., ٢٠١٠).***

Adiponectin is the most abundant circulating adipokine and modulates a wide array of biological functions. It was demonstrated to improve insulin resistance and play a role in the prevention of atherosclerosis. In addition to the above actions, adiponectin has several anti-inflammatory effects ***(Yamauchi et al., ٢٠٠٣).***

It facilitates the removal of early apoptotic cells by macrophages; it reduces Tumor necrosis factor-alpha (TNF-alpha) production in response to various stresses and antagonizes several of its inflammatory effects. Adiponectin is reported to exert its effects by interaction with specific receptors, termed AdipoR١ and AdipoR٢. AdipoR١ is abundantly expressed in skeletal muscles and

has a prominent action to promote lipid oxidation. AdipoR٢ is primarily transcribed in liver, where it enhances insulin sensitivity and reduces steatosis ***(Josson et al., ٢٠٠٥).***

Growing evidence suggested that adiponectin can regulate lipid and glucose metabolism and lipid content in hepatocytes. Adiponectin is also known to protect hepatocytes from injury ***(Wolf et al., ٢٠٠٤).***

Data indicates that adiponectin plays an anti-inflammatory role in both acute and chronic inflammatory liver diseases. The observed high plasma adiponectin could reflect an imbalance between its production by adipocytes and metabolism in the liver; that could be suggested from high adiponectin levels in chronic liver diseases might reflect one of the body's inflammatory mechanisms in this condition. The liver may play an important role in its catabolism and thus the elevated plasma levels in cirrhosis are, at least in part, due to decreased hepatic catabolism. Even true hepatic production might be another impact, since studies demonstrated that hepatocytes express significant amounts of adiponectin mRNA after injury ***(Tary et al., ٢٠١٠).***

Another suggested impact for the increased adiponectin in liver cirrhosis is altered hepatic extraction. The increased level of circulating adiponectin in cirrhosis seems to be independent of the underlying etiology. Previous studies demonstrated its elevation in cirrhosis due to hepatitis C, hepatitis B and Primary biliary cirrhosis ***(Tary et al., ٢٠١٠).***

Siagris et al., (٢٠٠٧) reported in his study is that adiponectin values of patients with chronic Hepatitis C virus infection (HCV) were higher than those of chronic hepatitis B virus infection (HBV) patients, and has been reported also that adiponectin is generally elevated in patients with chronic liver disease than in healthy controls. And in his study reported that there was no difference found in adiponectin values according to HCV genotype.

Tary et al., (٢٠١٠); reported in his study lack of a correlation between insulin resistance, when tested by homeostasis model assessment (HOMA) , and adiponectin levels in cirrhotic patients, and his findings might indicate that the pathogenesis of insulin resistance in cirrhosis differs from that in patients without liver disease.

Aim of the work

Adiponectin possess anti-inflammatory, insulin-sensitizing and anti-atherosclerotic properties. Aim of this study is to assess the levels of serum Adiponectin in different patients of Chronic Hepatitis C infection before, during and after treatment therapy and correlating these levels with markers of metabolic syndrome such as insulin resistance and correlating these levels with treatment therapy of chronic hepatitis C by interferon and ribavirin therapy.

Hepatitis C virus infection

Hepatitis C virus (HCV) is a virus that infects liver. Most people that are infected develop persistent infection. A proportion of people (٢٠-٥٠٪) develop progressive liver disease leading ultimately to liver cirrhosis, liver failure and hepatocellular carcinoma. An estimated ١٨٠ million people are infected worldwide ***(WHO, ٢٠١٠).***

In Egypt, the following sources of data on hepatitis C are available: death registries, nationwide epidemiological studies, laboratory reports and the blood donor registry data. The Ministry of Health and Population (MOPH) does have a system for the surveillance of ٢٦ communicable diseases including viral hepatitis with monthly reporting by all governments ***(MOHP, ٢٠٠٨).***

In ١٩٩٢, the prevalence of HCV in Egypt was reported to be ١٠,٨٪ among first-time blood donors ***(Kamel et al., ١٩٩٢).*** Since this discovery, many prevalence estimates of HCV have been reported, mostly from rural communities located in the northern Nile Delta ***(Saleh et al., ٢٠٠٨).***

For more than a decade, Egypt has been widely regarded as having an epidemic, with the highest recorded prevalence of HCV in the world.HCV is currently the most significant public health problem in Egypt ***(Alter et al., ٢٠٠٧).***

CAPMAS (Central Agency for Public Mobilization and Statistics) **at ٢٠٠٩,** estimates that population of Egypt in ٢٠٠٨ was ٧٧،١٥٦،٠٠٠ million and estimates the incidence was ٦,٥/١٠٠٠ persons per year.

The Egyptian Demographic Health Survey (EDHS) in ٢٠٠٩ involved a national probability sample of the resident Egyptian population, estimated an overall anti-HCV antibody prevalence of ١٤,٧٪. The number of Egyptians estimated to be chronically infected was ٩,٨ % ***(El-Zanaty et al., ٢٠٠٩).***

The number of new HCV infections, was ٥٣٧،٠٦٦ persons per year. Of these, approximately ٧٠،٠٠٠ would be in those aged below ٢٠ years ***(Miller et al., ٢٠١٠).***

More than ٩٠٪ of HCV isolates from Egyptian patients are of genotype ٤ variant, which is significant considering Egypt the highest worldwide prevalence of HCV (١٠-٢٠٪) and an overall seroprevalence that is ١٠-٢٠

folds higher than in the United States. In rural areas of Egypt, the prevalence of HCV reaches ٢٤٪. Subtype ٤a is the dominant variant found in Egypt ***(Sanaa et al., ٢٠٠٧).***

In the United States (U.S.), the prevalence of HCV infection between the years ١٩٩٩-٢٠٠٢ was ١,٦%, equating to about ٤,١ million persons positive for antibody to hepatitis C (anti-HCV), ٨٠٪ of who are estimated to be viremic. Hepatitis C is the principal cause of death from liver disease and the leading indication for liver transplantation in the U.S. ***(Marc et al., ٢٠٠٩).***

Hepatitis C is the major cause of chronic hepatitis in the United States. HCV infections accounts for ٢٠٪ of all cases of acute hepatitis and for more than ٤٠٪ of all referrals to active liver clinics. Of new infections, ٦٠٪ occur in intravenous drug users; less than ٢٠٪ of new cases are acquired through sexual exposure; and ١٠٪ are due to other causes, including occupational or perinatal exposure and hemodialysis. It was reported that HCV is largely responsible for the increase in the incidence of hepatocellular carcinoma (HCC) in the United States during the final decades of the ٢٠th century ***(Sandeep, Mukherjee et al., ٢٠١١).***